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[redacted]	**Statistical Analysis Plan**
	Sponsor: Novartis **Protocol number: CLEE011AIT01**

CLEE011AIT01 / NCT03439046

A phase IIIb, open-label, local, multicenter study of the molecular features of postmenopausal women with hormone receptor-positive (HR+) HER2-negative advanced breast cancer on first-line treatment with ribociclib plus letrozole and, in patients with a PIK3CA mutation, on second-line treatment with alpelisib plus fulvestrant (BioItaLEE)
- Final Analysis -

Authors	[redacted]
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Statistical Analysis Plan

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Document History

Status and Version	Release Date	Change Description	Reason/Comment
Draft Version 0.1	07NOV2023	N.A.	N.A.
Draft Version 0.2	10NOV2023	First draft version shared with the Sponsor after internal review.	N.A.
Draft Version 0.3	31JAN2024	Section 1.1 filled in with changes from the study protocol and Section 2 updated accordingly. Baseline, last administration and PFS2 definitions were updated in section 4.2 and additional details were also included for patients discontinuing due to progressive disease. Dictionaries version updated in section 4.3. Additional details were reported for management of liquid biopsy/TK1 serum level results analyses in section 4.4.2. Specifications about sample to be considered for BAS-EXT definition were included in section 5. Additional details were provided for study disposition in section 6.1 and for background and demographic characteristics analyses in section 6.2. New groups for ctDNA and TK1 were included for the analyses in section 6.3.1 together with a focus on EOT samples was added. Section 6.2 renumbered according to changes described in section 1.1 after removal some endpoints. New groups for TK1 were included for the analyses in section 6.3.2.1 together with TK1 analysis within ctDNA groups focusing on	Internal and Sponsor review

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Statistical Analysis Plan

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Protocol number: CLEE011AIT01

Status and Version	Release Date	Change Description	Reason/Comment
		categories defined considering C1D15 and C2D1. [redacted] Average daily dose definition, additional details for patients who finished the study due to Sponsor decision were included in Section 6.4.1 while the adjusted exposure and, consequently, DI and RDI for fulvestrant were removed. Section 6.4.3 according to AESI identification and relative appendices 8.1 and 8.2 were included. Section 6.4. were updated to provide conversion for HbA1c and to define the calculation of CTCAE grade based on laboratories values collected and relative appendix 8.3 was included.	
Draft Version 0.4	05MAR2024	Further details included in section 6.1 (study completion meaning, rephrase statements and inclusion of other prior medication according to data collected in "PRIOR AND CONCOMITANT" eCRF page), 6.3.1 (classification according to mutational status at EOT and swimmer plot for extension phase), 6.3.2.1 (inclusion of new category for complete TK1 dynamic change), [redacted] and 6.5.2 (related to antineoplastic treatments after the discontinuation of study treatment included). Minor change for adverse events in section 6.4.3 (Drop most common selection when request and in section 6.4.4 (scheduled timepoint of collection rephrased in Table 6.4.4-5).	Internal and Sponsor review
Draft Version 0.5	25MAR2024	Description if coagulation test at screening in section 6.2 updated to have summary for INR	Sponsor's review

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Status and Version	Release Date	Change Description	Reason/Comment
		and only listed value for aPTT and PT due to different unit of measurement (ratio, second). Inclusion of patients' classification of interest in the swimmer plot for extension in section 6.3.1. [redacted]	
Draft Version 0.6	10APR2024	Minor Changes in section 6.3.1.	Sponsor review
Final Version 1.0	11APR2024	First final release.	Sponsor's approval
Draft Version 1.1	23APR2024	Mutational dynamic change and complete mutational dynamic change for CORE phase are updated in section 6.3.1 as well as the mutational status categories to be considered in the swimmer plot for extension phase. No limit of detection is considered for VAF.	Data Review Meeting discussion
Final Version 2.0	23APR2024	Second final release.	Sponsor's approval

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Authorization

The signatures on this page indicate review and approval of the Statistical Analysis Plan, version 2.0, dated 23APR2024.

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Statistical Analysis Plan

Sponsor: Novartis

Protocol number: CLEE011AIT01

TABLE OF CONTENTS

LIST OF ABBREVIATIONS **8**

1. INTRODUCTION **12**

1.1. CHANGES FROM THE STUDY PROTOCOL 12

2. STUDY OBJECTIVES AND ENDPOINTS **12**

3. BACKGROUND AND RATIONALE **15**

3.1. OVERALL STUDY DESIGN AND PLAN DESCRIPTION 15

3.2. SELECTION OF STUDY POPULATION 18

3.3. TREATMENT 19

3.3.1. Treatment Administered 19

3.3.2. Method of Assigning Patients to Treatment Groups 20

3.3.3. Prior and Concomitant Therapy 21

3.4. SCHEDULE OF TIME AND EVENTS 22

3.5. SAMPLE SIZE AND POWER ESTIMATION 31

4. DEFINITIONS AND GENERAL METHODOLOGY **31**

4.1. GENERAL METHODOLOGY 31

4.2. DEFINITIONS 31

4.3. CODING OF THERAPIES AND MEDICAL TERMS 40

4.4. HANDLING OF DROP-OUTS OR MISSING DATA 41

4.4.1. Missing or Partial Dates 41

4.4.2. Handling of Missing Data/Imputation/Censoring Rules 42

4.4.3. Handling of Drop-Out Patients 44

4.5. MULTIPLE COMPARISON/MULTIPLICITY 44

4.6. MULTICENTRE STUDIES/CENTER POOLING 44

5. ANALYSIS POPULATIONS **44**

6. STATISTICAL METHODOLOGY **45**

6.1. STUDY PATIENTS 45

6.2. BACKGROUND AND DEMOGRAPHIC CHARACTERISTICS 47

6.3. EFFICACY EVALUATION 56

6.3.1. Primary efficacy analysis 56

6.3.2. Secondary efficacy analysis 63

6.3.2.1. TK1 serum levels and association with clinical outcome 63

6.3.2.2. ctDNA alterations in long responders and early progressors 66

6.3.2.3. Mutational alterations in screening ctDNA and tissue sample in de novo and recurrent patients 67

6.3.2.4. Agreement between liquid biopsies and tissue samples 68

6.3.2.5. Clinical efficacy of study treatment 70

[redacted] 72

6.3.4. Measurement of Treatment Compliance 74

6.4. SAFETY EVALUATION 74

6.4.1. Extent of Exposure 75

6.4.2. Concomitant medications 81

6.4.3. Adverse Events 82

6.4.4. Laboratory parameters 85

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

6.4.5. Vital signs/Physical examination 88
6.4.6. Other safety parameters 88
6.5. SUBGROUP ANALYSES 89
6.6. INTERIM ANALYSIS AND DATA MONITORING 89

7. REFERENCES 93

8. APPENDIX 93
8.1. PREFERRED TERM TO IDENTIFY ADVERSE EVENT OF SPECIAL INTEREST (AESI) FOR RIBOCICLIB 93
8.2. PREFERRED TERM TO IDENTIFY ADVERSE EVENT OF SPECIAL INTEREST (AESI) FOR ALPELISIB 130
8.3. LABORATORY PARAMETERS AND CORRESPONDING CTCAE V4.03 TERM THAT WILL BE CONSIDERED IN THE ANALYSIS 133

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	ALanine aminoTransferase/glutamic pyruvic transaminase/GPT
aPTT	activated Partial Thromboplastin Time
AST	ASpartate aminoTransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BAS	Biomarker Analysis Set
BMI	Body Mass Index
BOR	Best Overall Response
CxDxx	Cycle x, Day xx (referred to patients' treatment)
CBR	Clinical Benefit Rate
CI	Confidence Interval
CNV	Copy Number Variation
CR	Complete Response
ctDNA	circulating tumor DNA
DI	Dose Intensity
DFI	Disease-Free Interval
DNA	Deoxyribonucleic Acid
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report/Record Form
EoS	End of Study

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

EoT	End of Treatment
ER	Estrogen Receptor
FAS	Full Analysis Set
HR+	Hormone Receptor (PR or ER), HER2-
INR	International Normalized Ratio
LHRH	LH Releasing Hormone
LOD	Limit of Detection
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	Mammalian Target of Rapamycin
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria Adverse Event
NGS	Next Generation Sequencing analysis
NOPD	Non-Protocol Deviation
ORR	Overall Response Rate
PD	Progressive Disease
PD	Protocol Deviation
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PFS2	Progression-Free Survival on the second line treatment
PgR	Progesterone Receptor
PT	Preferred Term
PTA	Post-Trial Access
PTT	Partial Thromboplastin Time
PR	Partial Response

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Q1	First Quartile
Q2	Second Quartile, i.e., Median value
Q3	Third Quartile
QD	Quaque Die, one a day
QTcF	QT corrected interval using Fridericia formula
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Set
SD	Stable Disease
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
TBL	Total BiLirubin
TEAE	Treatment-Emergent Adverse Event
TEAESI	Treatment-Emergent Adverse Event of Special Interest
TESAE	Treatment-Emergent Serious Adverse Event
TFI	Treatment-Free Interval
TK1	Thymidine Kinase 1
[redacted]	[redacted]
TTFAR	Time To First Alpelisib Reduction
TTFRR	Time To First Ribociclib Reduction
TTP	Time To Progression
TTSAR	Time To Second Alpelisib Reduction

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

TTSRR	Time To Second Ribociclib Reduction
ULN	Upper Limit of Normality
UNK	Unknown
VAF	Variant Allelic Frequency = Molecular frequency
WHO-DD	World Health Organization Drug Dictionary

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

[redacted]	**Statistical Analysis Plan**
	Sponsor: Novartis
	Protocol number: CLEE011AIT01

1. INTRODUCTION

The present Statistical Analysis Plan (SAP) is aimed to detail the statistical analysis foreseen for the final analysis of the CLEE011AIT01 study. It is based on the protocol version v05, dated April 19th, 2023.

Both data collected during the core phase of the study and data collected during the extension phase will be taken into account.

1.1. Changes from The Study Protocol

The following changes from the study protocol will be implemented in the final analysis:

- The secondary objectives "*To evaluate mutational burden at baseline, its changes over time on ctDNA and its correlation with outcome*" and "*To evaluate tumor microenvironment before and after treatment*" will not be assessed, neither in the Core phase nor in the Extension phase. Both these objectives are based on the evaluation of tissue samples collected at the timepoints of interest, and only quite few tissue samples have been collected at the EOT evaluation, since collection was based on feasibility and patient consent. Basal Tumor Mutational Burden/Microenvironment just before therapy, in light of the evidence emerged after protocol finalization, is not very informative in the context of target therapy, as in immunotherapy for example.
- Moreover, due to the small sample size in the extension phase, the objectives "To identify patterns and follow the evolution of ctDNA alterations associated specifically to "long responders" and to patients with early progression (i.e., progressed at first imaging evaluation).", "To assess mutational and gene aberrations across different patient profiles" [redacted] In addition, the objective "To evaluate correlations between blood and tissue samples" will not be applied in the extension phase due to the lack of tissue sample and the small sample size.

2. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	VARIABLES	ENDPOINTS
Primary objective(s): **CORE PHASE:** To identify circulating tumor DNA (ctDNA) alterations, how they evolve, and evaluate their possible association with clinical outcome in the ribociclib + letrozole phase of treatment.	NGS analysis results on liquid biopsy over scheduled timepoints. Genes with any hotspot mutation, VAF of mutated allele. Occurred documented disease progression and/or deaths due to any cause.	**Primary endpoint(s):** **CORE PHASE:** Multiple gene assessments such as but not limited to RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53 and PTEN and their association with clinical outcome in the ribociclib + letrozole phase of treatment.

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[redacted]

Statistical Analysis Plan

Sponsor: Novartis

Protocol number: CLEE011AIT01

OBJECTIVES	VARIABLES	ENDPOINTS
EXTENSION PHASE: To identify circulating tumor DNA (ctDNA) alterations, how they evolve, and evaluate their possible association with clinical outcome in the alpelisib + fulvestrant phase of treatment.	NGS analysis results on liquid biopsy over scheduled timepoints. Genes with any hotspot mutation, VAF of mutated allele. Occurred documented disease progression and/or deaths due to any cause.	**EXTENSION PHASE:** Multiple gene assessments such as but not limited to RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53 and PTEN and their association with clinical outcome in the alpelisib + fulvestrant phase of treatment.
Secondary objective(s)[(a)]: **CORE PHASE:**		**Secondary endpoint(s):** **CORE PHASE:**
• To evaluate serum thymidine kinase 1 (TK1) activity over time as blood marker of proliferation and its association with clinical outcome.	TK1 serum levels over scheduled timepoints. Occurred documented disease progression and/or deaths due to any cause.	• Measurement of TK1 activity in serum and its correlation with clinical outcome in the ribociclib + letrozole phase of treatment.
• To identify the patterns and follow the evolution of ctDNA alterations associated specifically to “long responders” (i.e., Time to Progression > 25 months) and to patients with early progression (i.e., progressed at first imaging evaluation).	NGS analysis results on liquid biopsy over scheduled timepoints. Genes with any hotspot mutation, VAF of mutated allele.	• Multiple gene assessments such as but not limited to RB1, ESR1, CCND1, CDKN2A, PIK3CA, TP53 and PTEN in “long responder” patients and in those with early progression and their differences in the ribociclib + letrozole phase of treatment.
• To assess mutational and gene aberrations across different patient profiles.	NGS analysis results on liquid biopsy at screening. Genes with any hotspot mutation, VAF of mutated allele. NGS analysis results on tumor tissue sample at screening. Genes with any hotspot mutation, VAF of mutated allele.	• Differences in mutations and gene alterations will be assessed based on baseline samples (ctDNA and tissue) and compared across different patient profiles (i.e., newly diagnosed vs. recurrent disease) in the ribociclib + letrozole phase of treatment.
• To evaluate correlations between blood and tissue samples.	NGS analysis results on liquid biopsy at screening. Genes with any hotspot mutation, VAF of mutated allele. NGS analysis results on tumor tissue sample at screening. Genes with any hotspot mutation, VAF of mutated allele.	• Comparison between alterations detected through liquid biopsy and through tissue biopsy at baseline and at progression in the ribociclib + letrozole phase of treatment.

[redacted]

Statistical Analysis Plan

Sponsor: Novartis

Protocol number: CLEE011AIT01

OBJECTIVES	VARIABLES	ENDPOINTS
• To evaluate the safety and tolerability of ribociclib + letrozole in postmenopausal women with HR+, HER2- advanced breast cancer on first-line treatment.	Treatment emergent adverse events	• Adverse Events (AE), Grade 3/4 AEs & Serious Adverse Events (SAE) during treatment with ribociclib + letrozole.
• To assess the clinical efficacy of ribociclib + letrozole.	Overall tumor responses over time. Occurred disease progressions and/or death due to study disease.	• Time-to-Progression (TTP) (RECIST 1.1), based on investigators' assessment. • Overall response rate (ORR) as defined by RECIST 1.1 for patients with measurable disease. • Clinical Benefit Rate (CBR) as defined by RECIST 1.1, including patients with Complete Response (CR), Partial response (PR), Stable Disease (SD) and Non-CR/Non-Progressive Disease (PD) > 24 weeks.
EXTENSION PHASE:		**EXTENSION PHASE:**
• To evaluate the safety and tolerability of alpelisib + fulvestrant in postmenopausal women with HR+, HER2- advanced breast cancer.	Treatment Emergent adverse events.	• Adverse Events (AE), Grade 3/4 AEs & Serious Adverse Events (SAE) during treatment with alpelisib + fulvestrant.
• To assess the clinical efficacy of alpelisib + fulvestrant as a single treatment combination, and as one of two subsequent-line therapies (ribociclib + letrozole followed by alpelisib + fulvestrant) (PFS2 - PFS on second line treatment).	Overall tumor responses over time. Occurred disease progressions and/or death due to study disease. Occurred disease progressions in second line treatment and/or death due to any cause.	• Time-to-Progression (TTP) (RECIST 1.1), based on investigators' assessment. • Overall response rate (ORR) as defined by RECIST 1.1 for patients with measurable disease. • Clinical Benefit Rate (CBR) as defined by RECIST 1.1, including patients with Complete Response (CR), Partial response (PR), Stable Disease (SD) and Non-CR/Non-Progressive Disease (PD) > 24 weeks. • Progression Free Survival on the second line treatment

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OBJECTIVES	VARIABLES	ENDPOINTS
		(PFS2), based on investigators' assessment using RECIST 1.1.
[redacted]		

(a) [redacted]
Moreover, due to the small sample size in the extension phase, the objectives "To identify patterns and follow the evolution of ctDNA alterations associated specifically to "long responders" and to patients with early progression (i.e., progressed at first imaging evaluation).", "To assess mutational and gene aberrations across different patient profiles" [redacted] In addition, the objective "To evaluate correlations between blood and tissue samples" will not be applied in the extension phase due to the lack of tissue sample and the small sample size.

3. BACKGROUND AND RATIONALE

Study background and rationale, in terms of overview of breast cancer, introduction to investigational treatments, involvement of PIK3CA pathway in breast cancer, clinical pharmacokinetics, as well as rationale of core and extension phases and of study design, are detailed in the study protocol, sections *1 – Background* and *2 – Rationale*.

3.1. Overall Study Design and Plan Description

This is a multicenter, local, open-label, single-arm trial that has enrolled 287 patients in the core phase at 47 Italian sites.

Patients are treated, in the core phase, with ribociclib and letrozole in first line until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor or lost to follow-up, whichever occurs first.

Following treatment discontinuation, patients with PIK3CA mutations enter an extension phase and undergo treatment with alpelisib + fulvestrant in second line until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination

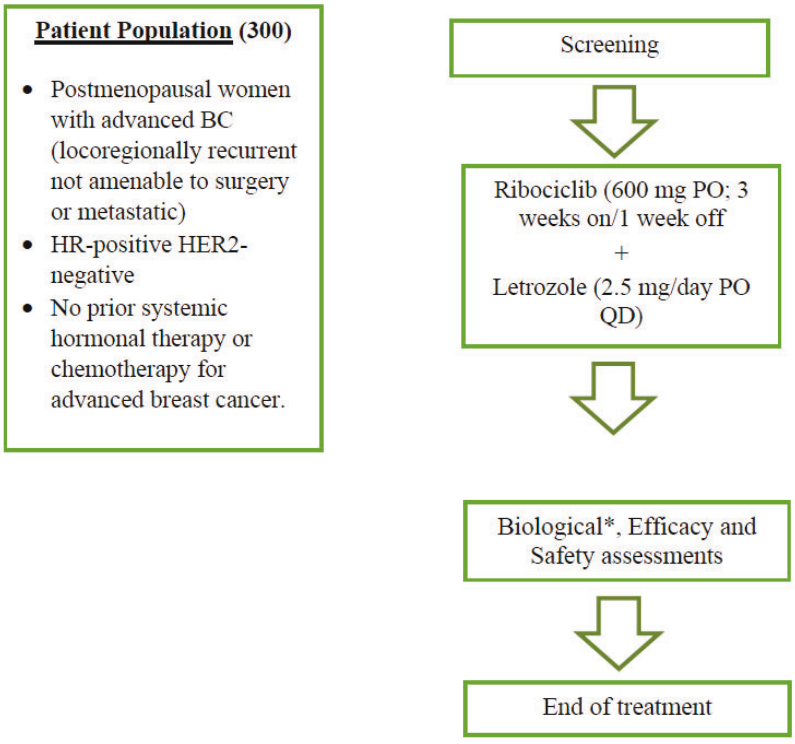
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by sponsor or lost to follow-up, whichever occurs first. Second line treatment is defined as the second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e., even in absence of progression).

In order to investigate the mechanisms of response and resistance to therapy with ribociclib in combination with letrozole, and to therapy with alpelisib in combination with fulvestrant, biological samples of blood and tumor tissue have been collected as foreseen by the study protocol, sections *4 - Study design* and *7 - Visit Schedule and assessments*.

The study design for the core and the extension phases is graphically represented in the figures below reported.

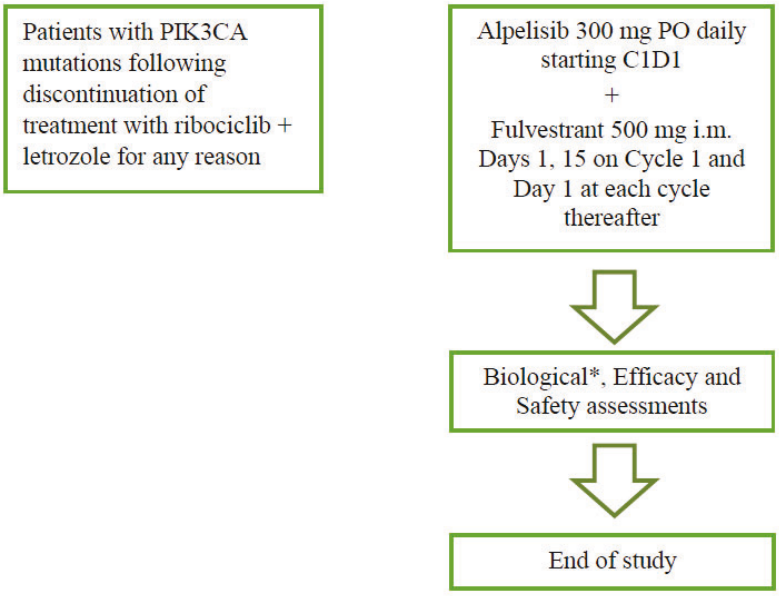
Figure 3.1-1.1 – Study design for the Core phase



*See Figure 3.1-2 for details

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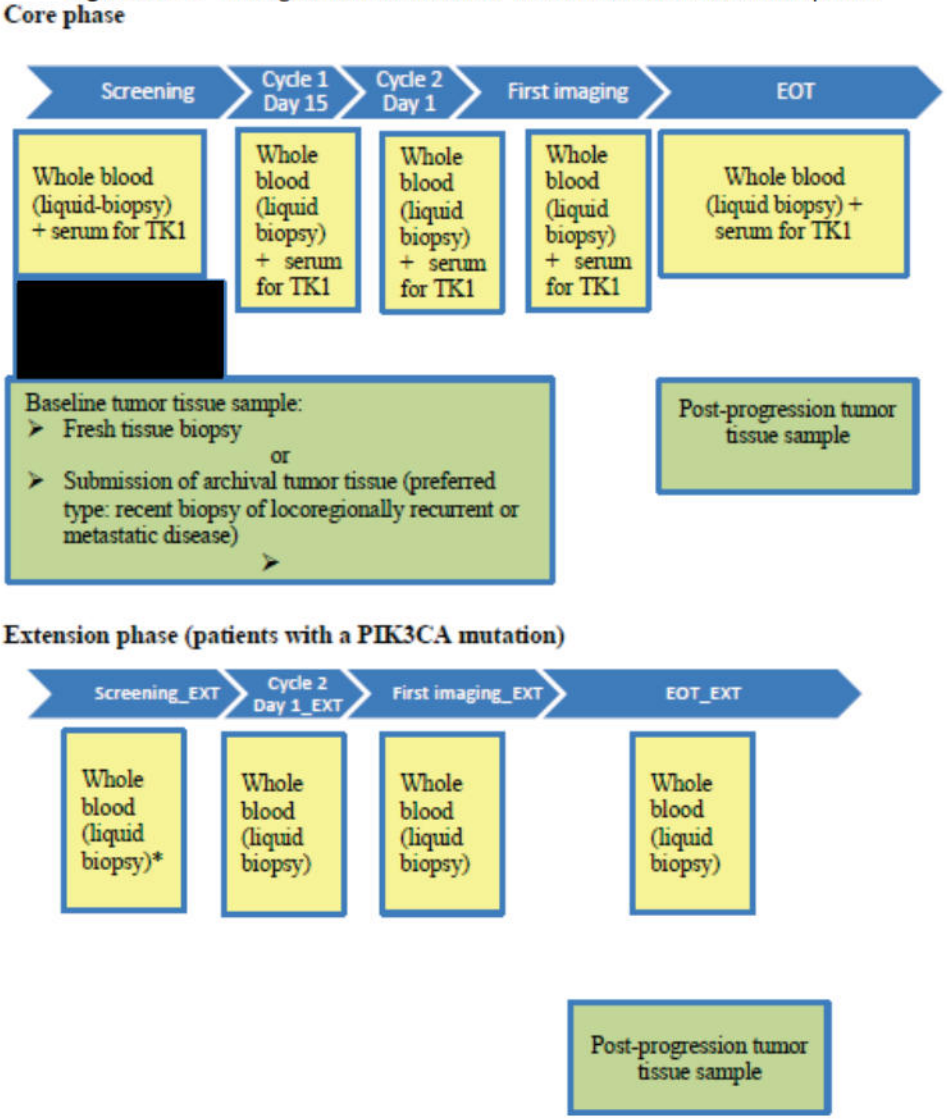
Figure 3.1-1.2 – Study design for the Extension phase



*See Figure 3.1-2 for details

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Figure 3.1-2 – Biological assessments for the Core and the Extension phase



*If not already collected at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form

3.2. Selection of Study Population

For the Core phase, the study population is made up of women in post-menopausal status with HR+, HER2- advanced (locoregionally recurrent not amenable to surgery or metastatic) breast cancer who have not received any prior agent for treatment of advanced disease. These patients have undergone treatment with ribociclib and letrozole.

For the Extension phase, the study population is made up of patients with PIK3CA mutations who discontinue therapy with ribociclib + letrozole during the core phase and subsequently undergo treatment with alpelisib + fulvestrant in second line. Second line treatment is defined in this protocol

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as the second therapy administered to the patient after first line treatment with ribociclib and letrozole, independently from the reason of discontinuation (i.e., even in absence of progression).

The investigator must ensure that the patient meets all the inclusion criteria and none of the exclusion criteria for enrolment in the study. A complete list of all inclusion/exclusion criteria is provided in Sections *5.2 - Inclusion criteria* and *5.3 - Exclusion criteria* of the study protocol respectively.

3.3. Treatment

3.3.1. Treatment Administered

For this study, the term **investigational drug** refers to the Novartis study drugs ribociclib and alpelisib for the Core and the Extension phases respectively. The other drugs to be used in this study are letrozole and fulvestrant.

Study treatment in this protocol refers to the combinations of investigational drug (ribociclib) + letrozole (Core phase) and investigational drug alpelisib + fulvestrant (Extension phase).

Ribociclib (200 mg tablets) and alpelisib (50 mg and 200 mg tablets) is supplied by Novartis as individual patient supply in packaged boxes. Letrozole (Femara) and fulvestrant is provided by Novartis.

Core phase

- Ribociclib (LEE011) 600 mg is given orally once a day on days 1-21 of each 28-day cycle. On days 22 - 28, ribociclib is not given ("rest days").
- Letrozole 2.5 mg is given orally as per Summary of Product Characteristics (SmPC) once a day on a continuous daily schedule (days 1-28 of each 28-day cycle). There is no "rest" in the letrozole schedule.

Study treatment Core phase is administered as a flat-fixed dose (starting doses: ribociclib 600 mg QD 3 weeks on/1 week off; letrozole 2.5 mg QD continuously), and not by body weight or body surface area. Further details on the correct administration way are available in section *6.1.2.1 - Ribociclib + letrozole* of the study protocol.

Patients may continue study treatment until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor, lost to follow-up or technical problems, whichever event occurs first.

For patients who do not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions are either recommended or required to allow patients to continue the study treatment. The allowed dose modifications are summarized in the study protocol, section *6.3 – Ribociclib dose modifications guidelines*. No dose re-escalation is permitted.

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring discontinuation (please refer to the study protocol, section *6.3 - Dose modifications*), treatment must be

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discontinued. In the case of ribociclib being withheld at Cycle (x) D1 based on investigator's judgement, the patient should reinitiate ribociclib on a 3-week on/1-week off schedule once the assessment(s) are within acceptable levels according to Section *6.3 - Dose Modifications* of the study protocol. The visit schedule should be adjusted based on the ribociclib treatment schedule. In the case of ribociclib being withheld for < 7 days during any cycle, patient should reinitiate ribociclib to complete the 21-calendar-day treatment (3 weeks on) followed by 1-week off schedule. In the case of ribociclib being withheld for ≥ 7 days during any cycle, patient should reinitiate ribociclib to a new 28 calendar day treatment schedule (3 weeks on/1 week off) once the assessment(s) are within acceptable levels according to Section *6.3 - Dose Modifications* of the study protocol. The visit schedule should be adjusted based on the ribociclib treatment schedule.

Dose reductions are not permitted for letrozole. In cases where letrozole is required to be permanently discontinued, the patient must be discontinued from the study.

Extension phase

- Alpelisib is administered orally at dose of 300 mg once continuously starting from C1D1.
- Fulvestrant 500 mg is given as intramuscular injection on Days 1 and 15 of Cycle 1, and on Day 1 of each cycle thereafter in a 28-day cycle.

Alpelisib is dosed on a flat scale of 300 mg/day and not by weight or body surface area. There are no breaks between dosing cycles. Further details on the correct administration way are available in section *6.1.2.2 – Alpelisib + fulvestrant* of the study protocol.

Patients with PIK3CA mutations may continue study treatment until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor, lost to follow-up or technical problems, whichever event occurs first.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria [NCI-CTCAE v4.03]. If the administration of alpelisib is interrupted for reasons other than toxicity, then treatment with alpelisib may be resumed at the same dose.

A maximum of 2 dose reductions of alpelisib from the recommended starting dose may be allowed before considering discontinuation of alpelisib as stated in section *6.3.2 – Alpelisib + fulvestrant* of the study protocol.

3.3.2. Method of Assigning Patients to Treatment Groups

All patients enrolled in the Core phase of the study are treated with the combination of ribociclib and letrozole.

Following treatment discontinuation, patients with PIK3CA mutations will be treated with alpelisib + fulvestrant in second line for the Extension phase of the study.

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3.3.3. Prior and Concomitant Therapy

Core phase

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed.

The medications prohibited during the Core phase of the study treatment are described in the study protocol, section *6.4.3 - Prohibited concomitant therapy*. Briefly, strong inhibitors or inducers of CYP3A4/5, substrates of CYP3A4/5 with a narrow therapeutic index, medications with a known risk for QT prolongation, investigational and antineoplastic therapies different form the study treatment and herbal preparations/medications that are strong inhibitors or inducers of CYP3A4/5 are indicated as prohibited concomitant therapy.

Corticosteroids should be avoided except for topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections and A short duration (< 5 days) of systemic corticosteroids ≤ to the anti-inflammatory potency of 4 mg dexamethasone.

Medications to be used with caution during treatment with combined ribociclib and letrozole are mentioned in section *6.4.2 – Concomitant therapy requiring caution* of the study protocol. They are Moderate inhibitors or inducers of CYP3A4/5, Sensitive substrates of CYP3A4/5, Strong inhibitors of Bile Salt Export Pump, medications that carry a possible risk for QT prolongation, Sensitive substrates of the renal transporters, MATE1, and OCT2, BCRP, Sensitive substrates of BCRP and Substrates metabolized predominantly by CYP2C19 or CYP2A6 with a narrow therapeutic index.

Bisphosphonates and denosumab are generally allowed with the exception of therapy administered for the prevention of bone metastases. Prophylactic use of WBC growth factors with ribociclib is not recommended.

Palliative radiation is permitted and should not encompass more than 25% of irradiated bone marrow.

Antiemetic therapy can be used according to clinical guidelines for antineoplastic medications with low to minimal emetogenic potential for treatment and/or prevention of nausea and vomiting resulting from study treatment.

Extension phase

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed.

The medications prohibited during the Core phase of the study treatment are described in the study protocol, section *6.5.3 - Prohibited concomitant therapy*. Strong inducers of CYP3A4m, Inhibitors of Breast Cancer Resistance Protein (BCRP) efflux transporter and other investigational and antineoplastic therapies should be avoided during treatment with alpelisib.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Medications to be used with caution during combined alpelisib and fulvestrant treatment in this study are mentioned in section *6.5.2 – Concomitant therapy requiring caution and/or action* of the study protocol. These medications should be excluded from use if possible. They are Sensitive substrates for CYP3A4, CYP2C9 or CYP2B6 and/or which have a narrow therapeutic index and herbal medications.

Hyperglycemia is a common adverse event for PI3K inhibitors like alpelisib and should therefore be used with caution and patients closely monitored. Patients who develop hyperglycemia during the study should be treated according to the ADA (American Diabetes Association) guidance. It is recommended to start treatment with metformin. Chronic dosing of high levels of corticosteroids such as dexamethasone and prednisone may prolong or aggravate hyperglycemia.

Acid reducing agents (ARAs, e.g., proton-pump inhibitors, H2-antagonists and antacids) are permitted as long as they are taken after food. The use of bisphosphonates/denosumab regardless of indication is allowed provided subjects are on stable doses for at least 2 weeks prior to enrollment. Stable dose should be maintained during the treatment period.

Hematopoietic growth factors may be used according to American Society of Clinical Oncology (ASCO) guidelines.

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required.

3.4. Schedule of Time and Events

For the schedule of time and events, see section *7 - Visit schedule and assessments* of the study protocol. The visit evaluation schedule for the Core and the Extension phases as reported in Tables 3.4-1 and 3.4-2 respectively.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Table 3.4-1 – Visit evaluation schedule - Core phase

	Protocol Section	Screening phase	Treatment phase									End of study treatment	Follow up	
Visit name		**Screening - 28 days to day1**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Subsequent visits (every 3 cycles, i.e. C9D1, C12D1, C15D1…)**	**End of study treatment[1]**	**30 day Safety follow-up[2]**	**3 months Post treatment follow up[9]**
Screening														
Informed consent	11.3	X												
Inclusion/exclusion criteria	5.2, 5.3	X												
Patient history														
Demography	7.1.1.3	X												
Medical history including post menopausal status	7.1.1.3	X												
Diagnosis and extent of cancer	7.1.1.3	X												
Prior antineoplastic therapy-medication	7.1.1.3	X												
Prior antineoplastic therapy-radiotherapy	7.1.1.3	X												

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

	Protocol Section	Screening phase	Treatment phase									End of study treatment	Follow up	
Visit name		**Screening - 28 days to day1**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Subsequent visits (every 3 cycles, i.e. C9D1, C12D1, C15D1…)**	**End of study treatment[1]**	**30 day Safety follow-up[2]**	**3 months Post treatment follow up[9]**
Prior antineoplastic therapy-surgery	7.1.1.3	X												
Prior and concomitant medication	7.1.1.3	X	Continuous – up to 30 days after last dose											
Surgical and medical procedures	7.1.1.3	X	Continuous – up to 30 days after last dose											
Physical examination														
Physical examination	7.2.3.1	X	X		X		X	X	X	X	X	X		
ECOG-PS	7.2.3.4	X	X		X		X	X	X	X	X	X		
Height	7.2.3.3	X												
Weight	7.2.3.3	X			X			X		X	X	X		
Vital signs	7.2.3.2	X	X		X		X	X	X	X	X	X		
Laboratory assessments														
Hematology (see Table 7.5)	7.2.3.5	(-14 days to day 1)		X	X	X	X	X	X	X	X	X		
Chemistry (see Table 7.5)	7.2.3.5	(-14 days to day 1		X	X	X	X	X	X	X	X	X		

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

	Protocol Section	Screening phase	Treatment phase									End of study treatment	Follow up	
Visit name		**Screening - 28 days to day1**	**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Subsequent visits (every 3 cycles, i.e. C9D1, C12D1, C15D1…)**	**End of study treatment[1]**	**30 day Safety follow-up[2]**	**3 months Post treatment follow up[9]**
Coagulation (INR)	7.2.3.5	X	As clinically indicated											
Biological assessments														
Blood for liquid biopsy[3] and serum[3]	7.2.1.2	X		X	X[4]	At first imaging evaluation.						X[5]		
[redacted]														
Tumor tissue sample	7.2.1.1	X[6]										X[7]		
Tumor assessments														
Tumor assessment	7.2.2	X	Recommendation: every 12 weeks from start of study treatment[8]									X[10]		
Cardiac assessment														
ECG (standard 12 lead)	7.2.3.6	-5 days to day 1		X	X		As clinically indicated					X[11]		
Safety														
Adverse events	8	Continuous for up to 30 days after last dose of study treatment												
Treatment														
Ribociclib	6		Daily: Day 1-21											
Letrozole	6		Daily											
Discontinuation														
Antineoplastic therapies since												X	X	X

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

	Protocol Section	Screening phase	Treatment phase									End of study treatment	Follow up	
Visit name		Screening - 28 days to day1	C1D1	C1D15	C2D1	C2D15	C3D1	C4D1	C5D1	C6D1	Subsequent visits (every 3 cycles, i.e. C9D1, C12D1, C15D1…)	End of study treatment[1]	30 day Safety follow-up[2]	3 months Post treatment follow up[9]
discontinuation of study treatment														

[1] End of study treatment (EOT) visit should be done within 7 days from the last dose of study treatment and prior to initiating subsequent therapy or to continue therapy as commercially available drug. Patients with PIK3CA mutations could proceed to the extension phase to be treated with alpelisib + fulvestrant or, after study termination by sponsor, could access PSDS.

[2] Within 30 days of last dose of study treatment. Following treatment discontinuation, patients with PIK3CA mutations will be treated with alpelisib + fulvestrant.

[3] Liquid biopsy to analyze ctDNA and serum to analyze thymidine kinase 1 activity.

[4] It is recommended to collect C2D1 biological samples after 4 weeks from C1D1.

[5] Blood for ctDNA and TK1 should be collected for all patients who discontinue treatment excluded those who discontinue due to study termination by sponsor.

[6] Newly obtained tissue biopsy or an archival tumor tissue derived by a recent biopsy of the locoregionally recurrent or metastatic disease (bone biopsy are acceptable). In cases this is not clinically feasible, the submission of an archival tumor tissue of the primary tumor is acceptable.

[7] New tissue biopsy should be done only for patients who discontinue the treatment due to disease progression.

[8]. The first imaging evaluation must be done at 12 weeks ± 7 days in order to standardize the timing of First Imaging biological sample collection (whole blood for liquid biopsy and serum for TK1).

[9] Post treatment follow up is not required for patients who discontinue due to study termination by sponsor.

[10] Tumor assessment at end of study treatment is not required for patients who discontinue due to study termination by sponsor.

[11] ECG at end of study treatment is not required for patients who discontinue due to study termination by sponsor.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Table 3.4-2 – Visit evaluation schedule - Extension phase

		Treatment phase_EXT							End of study treatment _EXT	Follow up_EXT	
Visit name	**Protocol section**	**Screening_ EXT (-28 days to day -1)**	**C1D1 _EXT**	**C1D8 _EXT**	**C1D15_ EXT**	**C2D1 _EXT**	**C2D15_ EXT**	**Subsequent cycles_EXT (day 1)**	**End of study treatment[1] _EXT**	**30 day Safety follow-up[2]_EXT**	**3 months post-treatment follow-up_EXT**
Obtain extension informed consent	11.3	X									
Inclusion/exclusion criteria	5.2, 5.3	X									
Diagnosis and extent of cancer	7.1.1.3	X									
Prior and concomitant medication	7.1.1.3	Continuous – up to 30 days after last dose									
Surgical and medical procedures	7.1.1.3	Continuous – up to 30 days after last dose									
Physical examination											
Physical examination	7.2.3.1	X	X	X	X	X	X	As clinically indicated	X		
ECOG-PS	7.2.3.4	X				X		X	X		
Weight	7.2.3.3	X				X		X	X		
Vital signs	7.2.3.2	X	X	X	X	X	X	X	X		
Laboratory assessments											
Hematology (see Table 7.7)	7.2.3.5	(-14 days to day -1)	X		X	X		X	X		
Chemistry (full) (see Table 7.7)	7.2.3.5	(-14 days to day -1)				X			X		
Chemistry (partial)			X		X			X			

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

		Treatment phase_EXT							End of study treatment _EXT	Follow up_EXT	
Visit name	**Protocol section**	**Screening_ EXT (-28 days to day -1)**	**C1D1 _EXT**	**C1D8 _EXT**	**C1D15_ EXT**	**C2D1 _EXT**	**C2D15_ EXT**	**Subsequent cycles_EXT (day 1)**	**End of study treatment[1] _EXT**	**30 day Safety follow-up[2]_EXT**	**3 months post-treatment follow-up_EXT**
Fasting plasma glucose		(-14 days to day -1)									
Fasting or random plasma glucose			X	X	X	X	X	X	X		
HbA1C		(-14 days to day -1)	C2D1 and then every 3 cycles (i.e. C5D1, C8D1...)								
Fasting lipid panel		(-14 days to day -1)							X		
Fasting lipase and amylase		(-14 days to day -1)						C3D1 and then as clinically indicated	X		
Coagulation	7.2.3.5	(-14 days to day -1)	As clinically indicated								
Urine analysis	7.2.3.5	(-14 days to day -1)	As clinically indicated						X		
Biological assessments											
Blood for liquid biopsy	7.2.1.2	X[3]				X[4]	At first imaging evaluation.		X[5]		
Tumor biopsy[6]									X		
Tumor assessments											
Tumor assessment	7.2.2	X[8]	Recommendation: every 12 weeks from start of study treatment[7]						X		
Cardiac assessment											

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

		Treatment phase_EXT							End of study treatment _EXT	Follow up_EXT	
Visit name	**Protocol section**	**Screening_ EXT (-28 days to day -1)**	**C1D1 _EXT**	**C1D8 _EXT**	**C1D15_ EXT**	**C2D1 _EXT**	**C2D15_ EXT**	**Subsequent cycles_EXT (day 1)**	**End of study treatment[1] _EXT**	**30 day Safety follow-up[2]_EXT**	**3 months post-treatment follow-up_EXT**
ECG (standard 12 lead)	7.2.3.6	(-14 days to day -1)	As clinically indicated						X		
Cardiac Imaging (MUGA or Echo)		X	As clinically indicated						X		
Safety											
Adverse events	8	Continuous for up to 30 days after last dose of study treatment									
Treatment											
Alpelisib	6		Daily								
Fulvestrant	6		X		X	X		X			
Discontinuation											
Antineoplastic therapies since discontinuation of study treatment									X	X	X
Survival follow-up											X

[1] End of study treatment (EOT) visit should be done within 28 days of last dose of study drug and prior to initiating alpelisib in PSDS or a subsequent therapy.

[2] Within 30 days of last dose of study treatment.

[3] Liquid biopsy at screening is required only if not obtained at EOT of core phase or if obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent. form

[4] C2D1 biological samples should be collected 4 weeks from C1D1.

[5] Blood for ctDNA should be collected for all patients who discontinue the treatment.

[6] Newly obtained tissue biopsy should be done for patients who discontinue the treatment due to disease progression.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

[7] The first imaging evaluation must be done at 12 weeks ± 7 days in order to standardize the timing of first imaging biological sample collection (whole blood for liquid biopsy).

[8] Any imaging assessments already completed during the core phase of the trial (i.e., last evaluation or EOT visit) within 28 days prior to start of extension study treatment, including before signing the extension study ICF, can be considered as the baseline images for the extension study.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

3.5. Sample Size and Power Estimation

Sample size for the present study is aligned with other biomarker studies and is based on a feasibility analysis of the trial and relative timelines. The study is descriptive in nature and no formal statistical testing is necessary or applicable, therefore no formal statistical power calculations to determine sample size have been performed.

Considering the explorative nature, no α-adjustment for the analysis is required.

4. DEFINITIONS AND GENERAL METHODOLOGY

4.1. General Methodology

Statistical tables, listings and analyses will be produced using SAS® release 9.4 (64 bit) or later (SAS Institute, Inc., Cary, NC, USA).

The data from all sites will be pooled and summarized.

Results for Core and Extension phases will be presented separately in dedicated documents.

Continuous data will be summarized with n, mean, standard deviation (SD), median, q1 and q3, range (i.e., minimum and maximum values). Categorical data will be presented by absolute and relative frequencies (n and %) or contingency tables. The percentage calculation will be based on total values (i.e., count will be shown also in the missing category, unless otherwise specified).

Unless stated otherwise, a two-sided alpha level 0.05 will be considered. No alpha level adjustment will be carried out for primary and secondary outcome variables, unless otherwise specified.

Other details on statistical methodology are described in other section of the present document.

4.2. Definitions

The following definitions will be used in the present document:

Study Phases

As already mentioned, the present study is divided into a Core phase and an Extension phase.

In the **Core phase**, postmenopausal women with HR+, HER2- advanced breast cancer who have not received any prior agent for treatment of advanced disease are treated with ribociclib + letrozole and followed until discontinuation of treatment due to any cause.

In the **Extension phase** is focused on patients who discontinue the Core phase of the study and have PIK3CA mutations. These women enter the “second part” of the study and undergo treatment with alpelisib + fulvestrant in second line.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Core phase and Extension phase will be managed separately in the analysis.

Study Sub-phases

The following subphases are distinguished in Core and Extension phases respectively:

Core phase

- **Screening phase (day -28 – day 0)**

  The period started after the Informed Consent signature, during which screening assessments are done within 1 to 28 days prior to start of study treatment or within 5 days prior to start of study treatment for ECG and within 14 days prior to start of study treatment for laboratory assessments.

  According to the study protocol (section 7.1.1 "Screening"), the re-screening of patients before starting treatment is allowed. Therefore, more than one screening evaluation could exist regarding one or more parameters. For the present analysis, the screening value for each considered parameter will be defined as the last screening evaluation obtained for patients before the start of study treatment at C1D1.

- **Treatment phase (Day 1 – day of the last treatment administration)**

  The period during which the study treatment is administered. It starts with the first assumption of ribociclib/letrozole and ends with the last drug (ribociclib or letrozole) intake. In the core phase of the study, patients are treated with ribociclib + letrozole until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason.

- **End of Treatment**

  End of study treatment (EOT) visit should be done within 7 days from the last dose of study treatment and prior to initiating any subsequent therapy.

- **Follow-up phase**

  The period after the end of the treatment administration up to the end of study/end of core Phase, depending on patients' eligibility for the Extension phase. The follow-up phase is articulated on 2 evaluations: the safety evaluations planned within 30 days after the last dose of study treatment (focused on record adverse events and concomitant medications), and the 3 months post treatment visit/phone call in which the first antineoplastic therapy started since discontinuation of study treatment is collected.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Extension phase

- **Screening phase (day -28 – day -1)**

  The period started after the Extension phase Informed Consent signature (that should correspond to date of the EOT visit of the core phase), during which screening assessments are done within 1 to 28 days prior to start of the extension study treatment. ECG and laboratory assessments are required within 14 days prior to start study treatment extended phase. PIK3CA mutation for patients eligible to the extension phase must be determined in tumor tissue and/or plasma by a Novartis designated laboratory during the Core phase of the study (results of tissue samples obtained at screening or EOT of the Core phase, are acceptable).

  Re-screening of patients is only allowed once per patient. For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. Any imaging assessments already completed during the core phase of the trial (i.e., last evaluation or EOT visit) within 28 days prior to start of extension study treatment, including before signing the extension study ICF, can be considered as the baseline images for the extension study.

- **Treatment phase (Day 1 – day of the last treatment administration)**

  The period during which the study treatment is administered. It starts with the first assumption of alpelisib/fulvestrant and ends with the last drug (alpelisib or fulvestrant) intake. Extension C1D1 Visit has to be done at least 7 days after the discontinuation of ribociclib and letrozole assumed in the core phase. Patients with PIK3CA mutations continue study treatment until disease progression, death, unacceptable toxicity, physician's decision, subject's decision, protocol deviation, study termination by sponsor, lost to follow-up or technical problems, whichever event occurs first.

- **End of Treatment**

  End of study treatment (EOT) visit should be done within 28 days of last dose of study drug and prior to initiating alpelisib in PTA or a subsequent therapy.

- **Follow-up phase**

  The period after the end of the treatment administration up to the end of study. The follow-up phase is articulated on 2 evaluations: the safety evaluations planned within 30 days after the last dose of study treatment (focused on record adverse events and concomitant medications), and the 3 months post treatment visit/phone call in which the first antineoplastic therapy started since discontinuation of study treatment is collected.

Screening Failures

Patient who signs an informed consent form but fails to be started on treatment for any reason is considered a screen failure. The reason for not being started on treatment are entered on the Screening Phase Disposition Page pf both study phases. Both in Core and in Extension phase,

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

demography, informed consent, inclusion/exclusion criteria, death and withdrawal of consent, if applicable, are the only data collected for screening failures.

Definition of Baseline

Both in Core and in Extension phase, the baseline assessments are defined as the ones performed at screening visit and this will be used to compute changes from baseline that corresponds to changes from screening (applicable for laboratory, vital signs, ECG, TK1, VAF values).

In the Extension phase only, any imaging assessments already completed during the Core phase of the trial (i.e., last evaluation or EOT visit) within 28 days prior to start of extension study treatment, including before signing the extension study ICF, can be considered as the baseline images.

First/Last Administration of Study Treatment

The date of **first administration** of study treatment is defined as the first date when a non-zero dose of any component of study treatment is administered and recorded on the DAR eCRF page, both for Core phase and for Extension phase.

For example, focusing on the Core phase: if the 1st dose of ribociclib is administered on January 1st, 2018 and the 1st dose of letrozole is administered on January 2nd, 2018, then the date of first administration of study treatment is January 1st, 2018.

The date of first administration of study treatment in both study phases will also be referred to start of study treatment and is identified as C1D1.

The date of **last administration** of study treatment is defined as the last date when a non-zero dose of any component of study treatment was administered and recorded on the DAR eCRF page, both for Core phase and for Extension phase. Of note, for patients who complete the End of Treatment eCRF page due to “Study terminated by Sponsor”, in case of end date missing for the last record collected in the DAR eCRF page with non-zero dose, the date of treatment discontinuation reported in the End of Treatment eCRF page will be considered as end date of last record in the DAR eCRF page since , in these cases, the study treatment was stopped due to a study close out decided by Sponsor for rationale of study protocol amendment number 4.

For example, focusing on the Core phase: if the last dose of ribociclib is administered on January 1st, 2019, and the last dose of letrozole is administered on January 2nd, 2019, then the date of last administration of study treatment is January 2nd, 2019.

Patients discontinuing due to progressive disease

Patients discontinuing the Core phase due to progressive disease are subjects who discontinued the ribociclib + letrozole combination treatment due to progressive disease or death for study indication.

Both a clinical and a confirmed progression of disease will be considered in the present definition of progressive disease.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Study day

The study day describes the day of the event or assessment date, relative to the reference start date. The study phases will be managed separately; therefore, the reference date is defined as the first administration of the study treatment (i.e., C1D1) in both the study phases.

The study day will be calculated as the difference between the date of each considered efficacy/safety assessment and the start of study treatment (i.e., C1D1) plus 1 day.

If a considered event starts before the start of study treatment, the study day will be calculated as the difference between the date of the assessment and the start of study treatment. Therefore, the study day will be negative.

The study day will be displayed in patient data listings. It is not to be used in numerical computations.

Clinical outcome

In both the study phases, the clinical outcome will be assessed by means of the Progression-Free Survival (PFS).

Progression-Free Survival (PFS)

The progression-free survival is defined as the time, in months, from the date of start of the study treatment (i.e., C1D1 of each considered study phase) to the date of event defined as the first documented progression or death due to any cause, whichever comes first. Only imaging evaluations and deaths occurred prior to the start of any subsequent anticancer treatment or up to 30 days from the end date of the study treatment administration (whichever occurs first) will be considered as PFS events.

For subjects who do not experienced events the PFS time will be censored at the date of their last adequate tumor assessment collected during the considered study phase (i.e., the date of the last imagining evaluation performed up to end of the considered study phase/start of any subsequent therapy/30 days after the last administration of study treatment).For patients who perform no post-baseline tumor assessments and who did not die, PFS time will be censored at the C1D1 date of the considered study phase.

Subjects who withdraw consent from the study before disease progression or death (if death information is collected after withdrawal) will be censored at the last adequate tumor assessment before withdrawal of consent to the study.

Subjects who are lost to follow-up will be censored at the last adequate tumor assessment before they are lost to follow-up.

Determination of dates of PFS event and dates for censoring is summarized in Table 4.2-1 as follows.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Table 4.2-1 – PFS event and censoring method

Situation	Date of progression or censoring	Outcome
Documented progression of disease (PD)	Earliest date that indicates the disease progression before the start of any subsequent therapy/30 day after the last administration of study treatment.	PFS event
Clinical progression of disease	Date of last imaging evaluation performed before the study phase end/start of any subsequent therapy/30 day after the last administration of study treatment (i.e., within the considered period)	Censored
Death	Date of death if occurred before the start of any subsequent therapy/30 day after the last administration of study treatment	PFS event
Death after the start of any subsequent therapy/30 day after the last administration of study treatment without subsequent therapies/study phase end date	Date of last imaging evaluation performed before the start of any subsequent therapy/30 day after the last administration of study treatment/study phase end date (i.e., within the considered period)	Censored
No imaging assessment performed	Date of C1D1 of the considered study phase	Censored
Other (e.g., no PFS event, withdrawal of consent to study participation, lost to follow-up etc.)	Date of last imaging evaluation performed before the start of any subsequent therapy/30 day after the last administration of study treatment/ study phase end date (i.e., within the considered period)	Censored

Further details on PFS calculation and analysis are reported in Section 6.3.1 of the present document.

Clinical efficacy

In both the study phases, the clinical effect of study treatment (Core and Extension phases separately considered) will be assessed by means of the variables following defined.

Tumor Responses

The tumor evaluations are made locally according to the Novartis guideline version 3.2 (see Appendix 14.7 of the study protocol) based on RECIST criteria [1] and revised RECIST guidelines, version 1.1 [2]. No central review of imaging assessments will be done.

Patients' measurable, non-measurable and new lesions are evaluated at each scheduled timepoint as stated in study protocol, appendix 14.7 *Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1).*

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Only evaluations performed before to any subsequent therapy start or before to 30 days after the last administration of study treatment, whichever comes first, will be considered in each study phase.

The overall lesion response is defined as the combination of the patients' target, non-target and new lesion responses, defined according to RECIST 1.1 criteria. It is ranked as follows, from highest to lowest response:

- complete response (CR)
- partial response (PR)
- stable disease (SD)
- progressive disease (PD)
- unknown (UNK)

If the overall lesion response at any timepoint is "Non-CR/Non-PD" due to the presence of only non-target lesions, the patient lesion response will be considered as "Non-CR/Non-PD" disease.

The Best Overall Response (BOR) is the best response recorded for each patient from the start of the treatment (separately for each study phase) until confirmed disease progression/early discontinuation/start of any subsequent therapy/30 days after the last administration of study treatment, whichever occurs first. Patients without measurable lesions at baseline will also be considered. The best overall response usually is determined from response assessments undertaken while on treatment. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least one determination of CR; a patient who had a CR cannot subsequently have a lower status other than a PD, e.g., PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.
- PR = at least one determination of PR.
- SD = at least one SD assessment > 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD = progression after start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases.

The response achieved at the first performed imaging evaluation will be used to define the early response for all patients performing the first post-screening assessment up to 112 days after C1D1.

Based on the patients' best overall response during the Core phase of the study, the following rates are then calculated:

Overall Response Rate (ORR)

The overall Response Rate is defined as the proportion of patients with a best overall response of CR or PR.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Clinical Benefit Rate (CBR)

The Clinical Benefit Rate is defined as the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity considering duration of disease stabilization.

Time To Progression (TTP)

The time to progression is defined as the time, in months, from the date of start of the study treatment (i.e. C1D1 of the considered study phase) to the date of event defined as the first documented progression or clinical deterioration of patient's condition (inserted in the "End of Treatment disposition" eCRF page) or death due to underlying cancer (i.e., death inserted as due to "Study Indication" in the Death eCRF page), whichever comes first. Only PD (confirmed or clinical) and deaths due to underlying cancer occurred prior to the start of any subsequent anti-cancer treatment or within 30 days from the last administration of study treatment will be included in the analysis.

Patients without an event of interest will be censored on the date of their last tumor assessment (i.e., imaging assessment) prior to the start of any subsequent anti-cancer treatment or within 30 days after the last administration of study treatment.

For patients who performed no post-baseline tumor assessments and who did not die, TTP will be censored at the C1D1 date.

Determination of dates of TTP event and dates for censoring is summarized in Table 4.2-2 as follows.

Table 4.2-2 – TTP event and censoring method

Situation	Date of progression or censoring	Outcome
Documented progression of disease (PD)	Earliest date that indicates the disease progression before the start of any subsequent therapy/30 day after the last administration of study treatment/study phase end date (i.e., the first performed imaging evaluation during which the PD was observed)	TTP event
Clinical progression of disease	Date of discontinuation reported in the "End of Treatment disposition" eCRF page before the start of any subsequent therapy/30 day after the last administration of study treatment/ study phase end date (i.e., within the considered period)	TTP event
Death due to disease progression	Date of death if occurred before the start of any subsequent therapy/30 day after the last administration of study treatment/ study phase end date	TTP event

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Clinical progression of disease or death due to disease progression occurred after the start of any subsequent therapy/30 day after the last administration of study treatment/ study phase end date	Date of last imaging evaluation performed before the start of any subsequent therapy/30 day after the last administration of study treatment/ study phase end date (i.e., within the considered period)	Censored
Death due to reasons other than disease progression	Date of last imaging evaluation performed before the start of any subsequent therapy/30 day after the last administration of study treatment/ study phase end date (i.e., within the considered period)	Censored
No imaging assessment performed	Date of C1D1 of each considered study phase	Censored
Other (e.g., no TTP event, withdrawal of consent to study participation, lost to follow-up etc.)	Date of last imaging evaluation performed before the start of any subsequent therapy/30 day after the last administration of study treatment/study phase end date (i.e., within the considered period)	Censored

Further details on TTP calculation and analysis are reported in Section 6.3.2 of the present document.

Progression-Free Survival on second line treatment (PFS2)

The progression-free survival on second line treatment is defined as the time, in months, from the date of start of the study treatment of the Core phase (i.e., C1D1 of the ribociclib+letrozole treatment) to the date of event defined as the first documented progression on next-line treatment or death from any cause.

PFS2 will be calculated for the patients who undergo the Extension phase only. It is considered a surrogate for overall survival when the overall survival cannot be measured reliably, and it assesses the impact of the experimental therapy on next-line treatment.

For subjects who do not experienced events, the PFS2 time will be censored at the date of their last adequate tumor assessment collected during the Extension phase (i.e., the date of the last imagining evaluation performed up to end of the considered study phase/start of any subsequent therapy/30 days after the last administration of study treatment).For patients who perform no post-baseline tumor assessments and who did not die, PFS time will be censored at the last objective assessment performed during the Core phase.

Subjects who withdraw consent from the study before disease progression or death (if death information is collected after withdrawal) will be censored at the last adequate tumor assessment before withdrawal of consent to the study.

Subjects who are lost to follow-up will be censored at the last adequate tumor assessment before they are lost to follow-up.

Determination of dates of PFS2 event and dates for censoring is summarized in Table 4.2-3 as follows.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Table 4.2-3 – PFS2 event and censoring method

Situation	Date of progression or censoring	Outcome
Documented progression of disease (PD) during the Extension phase	Earliest date that indicates the disease progression before the start of any subsequent therapy/30 day after the last administration of study treatment.	PFS2 event
Clinical progression of disease during the Extension phase	Date of last imaging evaluation performed before the study phase end/start of any subsequent therapy/30 day after the last administration of study treatment	Censored
Death during the Extension phase	Date of death if occurred before the start of any subsequent therapy/30 day after the last administration of study treatment	PFS2 event
Death after the start of any subsequent therapy/30 day after the last administration of study treatment without subsequent therapies/study phase end date	Date of last imaging evaluation performed before the start of any subsequent therapy/30 day after the last administration of study treatment/study phase end date (i.e., within the considered period)	Censored
No imaging assessment performed in the Extension phase	Date of last imaging evaluation performed during the Core phase	Censored
Other (e.g., no PFS2 event, withdrawal of consent to study participation, lost to follow-up etc.)	Date of last imaging evaluation performed before the start of any subsequent therapy/30 day after the last administration of study treatment/ study phase end date (i.e., within the considered period)	Censored

Further details on PFS2 calculation and analysis are reported in Section 6.3.2 of the present document.

4.3. Coding of Therapies and Medical Terms

The World Health Organization Drug Dictionary (WHO-DD), version B3 Q1 2023 or later, will be used to code previous and concomitant medications.

The latest available version of Medical Dictionary for Regulatory Activities (MedDRA) will be used to code medical terms reported in the Medical History, prior and concomitant surgeries and Adverse Events eCRF pages. Version 26.0 will be applied.

All the coded terms should be updated using the latest version or the dictionaries available at the time of the analysis.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

4.4. Handling of Drop-Outs or Missing Data

4.4.1. Missing or Partial Dates

Missing and partial dates will be managed in the Core phase of the study only. In the Extension phase, dates will be presented as collected.

The imputation of partial dates will be performed only if the dates are involved in the computation of variables needed for the study analysis and if at least the year is present (i.e., no imputation will be performed if the date is completely missing).

If not otherwise specified, the following general assumptions will be made in case of partially missing information:

- In case of day missing, the day will be replaced with 15;
- In case of day and month missing, the day will be replaced with 1, the month with July.

However, the just mentioned general assumption will not be applied to the following variables:

AE onset/end date

Focusing on the AE onset date:

- If onset date is missing => the start date of of ribociclib + letrozole treatment (i.e., C1D1) will be imputed.
- If only the onset day is missing, it will be imputed:
    - the same day of the C1D1 date if the available AE onset month and year correspond to the start of treatment month and year;
    - the same day of the end of treatment date (see definition in section above) if the available AE onset month and year correspond to the end of treatment month and year and the AE end day is lower than 15.
    - 15 if the available AE onset month and year correspond to the end of treatment month and year and the AE end day is equal to or greater than 15.
- If onset day and month are both missing, the following values will be imputed:
    - Day and month of AE end date if the AE onset year corresponds to the year of C1D1 and the AE is concluded before or on the C1D1 date;
    - Day and month of C1D1 date if the AE onset year corresponds to the year of C1D1 and the AE is not concluded (i.e., if the AE end date is missing);
    - Day and month of AE end date if the AE onset year corresponds to the year of AE end, the AE end month is equal to or lower than 7 (i.e., is equal or before July) and the AE end day is equal to 1;
    - July 1st otherwise.

Focusing on the AE onset date:

- If AE end date is completely missing (i.e., in case of ongoing event) => the patient End of Study phase for the Core phase will be imputed.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Imaging Evaluation date

The last non-missing date among target, non-target and overall lesions evaluation performed at each considered timepoint (LR dataset) during the Core phase will be assumed as imaging evaluation performance date. In this way, the imaging evaluation date will be read as date during which the tumoral assessment process of the considered timepoint is completed.

4.4.2. Handling of Missing Data/Imputation/Censoring Rules

Patients will be included in each analysis based on available assessments. No methodology for missing data handling will be applied, unless otherwise specified.

Censoring rules will be applied to time-to-event endpoints (see section *6.3 Efficacy Evaluation* and section *6.4 Safety Evaluation* of the present document for further details).

Management of time scheduled

All nominal time points will be used for descriptive analysis by visit; no adjustment considering the actual date of assessments will be performed. Unscheduled visits will be not considered, unless otherwise specified.

For the efficacy analysis, the following methodologies will be applied:

- For patients' liquid biopsy and TK1 serum samples, the date of sample collection reported into eCRF/samples will be considered. The computed analysis day for each sample collection will be used to describe patients' adherence to the scheduled activities.

- Patients' imaging evaluations will be described by progressive order of evaluation (i.e., evaluation 1, evaluation 2, etc.). The computed analysis day for the first performed imaging evaluation will be used, in the Core phase of the study, to select the patients who reported a progressive disease at the first imaging evaluation performed up to 112 days after C1D1 (i.e., the early progressors).

Management of liquid biopsy/TK1 serum level results analyses

In both Core and Extension phases, liquid biopsy samples and TK1 serum samples will be properly handled to maximize the information. The following actions will be put in place for the final analysis:

First Imaging/EOT

In both study phases, data collected on first imaging/EoT samples could be adjusted according to the following Table 4.4.2-1 for patients who discontinued the treatment due to progressive disease (refer to definition in Section 4.2 above).

Table 4.4.2-1 – Management of liquid biopsy/TK1 serum sample at first imaging/EoT for patients experiencing a progression of disease during both the phases of the study

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Sample(s)			Action
First imaging	First imaging - unscheduled [(a)]	EoT	
x	-	x	No action required. All samples will be considered in the analysis.
x	x	x	No action required. All samples will be considered in the analysis.
x	x	-	• Results of first imaging-unscheduled sample will be duplicated for the EoT assessment if the EoT visit was performed within 30 days from the first imaging unscheduled sample collection. • No action required if the EoT visit was performed more than 30 days after the first imaging unscheduled sample collection.
x	-	-	• Results of first imaging sample will be duplicated for the EoT assessment if the EoT visit was performed within 30 days from the first imaging sample collection. • No action required if the EoT visit was performed more than 30 days after the first imaging sample collection.
-	x	x	No action required.
-	-	x	• Results of EoT sample will be duplicated for the first imaging assessment if the first imaging evaluation was performed up to 30 days before the EoT sample collection. • No action required if the first imaging evaluation was not performed or was performed more than 30 days before EoT sample collection.
-	x	-	• Results of first imaging-unscheduled sample will be duplicated for the EoT assessment if the EoT visit was performed within 30 days from the first imaging - unscheduled sample collection. • No action required if the EoT visit was performed more than 30 days after the first imaging-unscheduled sample collection.

X=valid sample available; -=no valid sample available.

[(a)] First imaging - unscheduled are samples collected more than 30 days after the performance of the first imaging evaluation.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

For patients who did not experience progression of disease during the Core phase (refer to definition in Section 4.2 above), liquid biopsy and TK1 serum samples collected at first imaging timepoint will be considered in the analysis without performing adjustment actions.

Liquid biopsy and TK1 serum samples collected at End of Treatment visit in both study phases will be excluded from the analysis for patients who do not experience a disease progression (refer to definition in Section 4.2 above). These EOT data will be listed only.

Core/Extension phases

Liquid Biopsy sample at screening during the Extension phase of the study is required only if not obtained at EOT of the Core phase or if it was obtained more than 28 days prior to the signature of the Extension Phase's Informed Consent form. For this reason, no adjustment will be done in case of Extension phase screening evaluation missing.

4.4.3. Handling of Drop-Out Patients

Patients will be included in the analysis based on available assessments, unless otherwise specified.

4.5. Multiple Comparison/Multiplicity

Not Applicable for the present analysis.

4.6. Multicentre Studies/Center Pooling

Not Applicable for the present analysis.

5. ANALYSIS POPULATIONS

The present analysis will be focused on the analysis sets defined in the study protocol in section *10.1 - Analysis Sets*. Therefore, the following analysis populations will be considered:

Core phase

- **Full Analysis Set (FAS)**: all patients who receive at least one dose of study medication defined as either ribociclib or letrozole.

- **Biomarker Analysis Set (BAS)**: all patients of the Full Analysis set who have an evaluable biomarker profile (i.e., both valid liquid biopsy and TK1 serum samples collected at screening) and who do not have violations of the main inclusion-exclusion criteria.

- **Safety Set (SAF)**: all patients who receive at least one dose of study medication defined as either ribociclib or letrozole, the same definition of the Full Analysis Set.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Extension phase

- **Full Analysis Set – Extension phase (FAS-EXT)**: all patients entering the extension phase who receive at least one dose of study medication defined as either alpelisib or fulvestrant.

- **Biomarker Analysis Set – Extension phase (BAS-EXT)**: all patients of the Full Analysis set of the Extension phase who have an evaluable biomarker profile (at least baseline samples) and who do not have violations of the main inclusion-exclusion criteria. For valid baseline biomarker sample will be considered a valid Liquid Biopsy sample collected at screening during the Extension phase or at EOT of the Core phase if it was obtained no more than 28 days prior to the signature of the Extension phase's Informed Consent form.
- **Safety Set– Extension phase (SAF-EXT)**: all patients entering the extension phase who receive at least one dose of study medication defined as either alpelisib or fulvestrant, the same definition of the Full Analysis Set– Extension phase.

6. STATISTICAL METHODOLOGY

Results for Core and Extension phases will be presented separately in dedicated documents.

6.1. Study Patients

For both study phases, patients' **screening disposition** will be summarized. The number of patients screened ((i.e., patients who signed a valid Informed Consent Form for the considered study phase) will be provided together with the number of patients who discontinued the screening sub-phase and the reasons for discontinuation. For screening failure patients, a summary of inclusion criteria not met/exclusion criteria met will be listed. Absolute and relative frequencies of re-screened patients will be described. Number of subjects enrolled in the study (i.e., subjects who complete the screening disposition and are eligible for the study enrolment) will also be summarized. Further details on collected written informed consent forms will be listed.

Focusing on the enrolled patients, the **patients' disposition** will be described providing a summary of the patients who complete or discontinue the study phase treatment and the reasons for treatment discontinuation. An analogous description will be provided considering the number of patients who complete or discontinue the study phase and a summary of the reasons underlying the study discontinuations. In case patients discontinued treatment due to 'Death' or 'Lost to follow-up' or 'Study Terminated by sponsor' the End of study eCRF page will not fill in and the same information collected in the End of treatment eCRF page will be considered also for the End of study. For the Core phase only, the number of patients eligible for the Extension phase will also be presented detailing the number of subjects with PIK3CA mutations who discontinue therapy with ribociclib + letrozole and the number of mutated patients who continue the next phase of the trial. Of note, in this case the study disposition provides information about the follow-up contacts performed by patients: a complete study disposition means that patient performed both the 30 day safety follow-up visit and the 3 months post-treatment follow-up contact (applicable only for patients who signed the protocol amendment 1 dated on 11-July-2018); a discontinued study disposition means that patient did not perform all the follow-up assessments scheduled after the end of treatment. Of note, for the Core

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

phase, also patients who entered in the extension phase will be considered as having complete study disposition even if some follow-up assessments could be not performed.

The number of patients reporting any **protocol deviation** collected during each considered study phase will be described, and the number of patients reporting each considered PD will be summarized. Analogous descriptions will be provided for the **non-protocol deviation** considered in the present analysis, i.e., those criteria leading to the exclusion from an analysis population, even if they do not themselves constitute a deviation from the study protocol, which are detailed in Table 6.1-1 and Table 6.1-2 for Core and Extension phases respectively. Protocol and non-protocol deviations will also be listed.

Table 6.1-1 – List of non-protocol deviations for the Core phase

Non-protocol deviations Code	Description	Exclusion from Analysis Population
NOPD01	Patients who did not receive at least one dose of study medication defined as either ribociclib or letrozole	FAS/BAS/SAF
NOPD02	Patient without valid liquid biopsy at baseline (screening visit)	BAS
NOPD03	Patient without valid TK1 serum sample at baseline (screening visit)	BAS

FAS = Full Analysis Set; BAS = Biomarker Analysis Set; SAF = safety Analysis Set; NOPD = Non-protocol-related deviation.

Table 6.1-2 – List of non-protocol deviations for the Extension phase

Non-protocol deviations Code	Description	Exclusion from Analysis Population
NOPD01EXT	Patients entering the extension phase who did not receive at least one dose of study medication defined as either alpelisib or fulvestrant	FAS-EXT/BAS-EXT /SAF-EXT
NOPD02EXT	Patient without valid liquid biopsy at baseline (i.e., at screening visit, at EOT of core phase or obtained up to 28 days prior to the signature of the Extension Phase's Informed Consent. form)	BAS-EXT

FAS-EXT = Full Analysis Set – Extension phase; BAS-EXT = Biomarker Analysis Set – Extension phase; SAF-EXT = safety Analysis Set – Extension phase; NOPD = Non-protocol-related deviation.

The number of patients included in each **analysis population** will be summarized.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

6.2. Background and Demographic Characteristics

Core phase

Background and demographic characteristics, vital signs, medical history and prior medications will be summarized descriptively for patients valid both for the FAS and for the BAS.

Demography & Disease and clinical characteristics

Demographic characteristics will be summarized focusing on age, race and ethnicity.

Age will be described both in continuous term and in categorical term presenting the following classes:

- <65 years vs. ≥65 years;
- <70 years vs. ≥70 years.

Patient distribution by **race** will consider all the indications collected in the eCRF page, i.e., Caucasian, Black, Asian, Native American, Pacific Islander, unknown and other. The **ethnicity** will be summarized too.

For women who are not 60 years old and who have not undergone bilateral oophorectomy, the **childbearing status** will be described calculating the time form the start date of amenorrhea to the start of the Core phase, the proportion of patients who performed FSH and/or Estradiol tests and a summary of FSH and Estradiol values.

The time from the amenorrhea start will be calculated, in years, as:

Time from amenorrhea start (years)= (date of C1D1 – date of amenorrhea start + 1 day)/365.25

Disease and clinical characteristics will be described by means of the variables defined as follows.

ECOG performance status at screening will be summarized with absolute and relative frequencies.

Diagnosis and extent of cancer will be described through the time elapsed (in years) from the initial diagnosis of disease to the start of the Core phase, the disease stage at initial diagnosis, the disease stage at study entry, the histological grade and the histological subtype.

The time from the initial diagnosis will be calculated, in terms of years, as:

Time from initial diagnosis (years)= (date of C1D1 – date of initial diagnosis + 1 day)/365.25

Both times will be summarized by means of the usual descriptive statistics.

Disease stage at initial diagnosis and at study entry will be grouped as follows:

- 0 => Stage 0
- I, IA, IB, IC => Stage I

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

- II, IIA, IIB, IIC => Stage II
- III, IIIA, IIIB, IIIC => Stage III
- IV, IVA, IVB => Stage IV

Patients will be classified also as de novo vs. recurrent (patients' disease status). De novo patients are defined as subjects who have the "date of first recurrence/progression" information (variable "*Date of diagnosis of advanced disease (locoregionally recurrent not amenable to surgery or metastatic)*") blank in the "Diagnosis and extent of cancer" eCRF page. For recurrent patients, the time elapsed (in months) from the diagnosis of advanced disease (locoregionally recurrent not amenable to surgery or metastatic) to the start of the Core phase will be also provided.

The time from the diagnosis of advanced disease will be calculated (in case of non-missing date only) as:

Time from the diagnosis of advanced disease (months)= (date of C1D1 – date of diagnosis of advanced disease + 1 day)/30.4375

Hormone receptors status will be described through absolute and relative frequencies of patients positive or negative in terms of HER2 receptor, Estrogen (ER) receptor, Progesterone (PgR) receptor and ER and PgR receptors together considered. Moreover, for HER2 receptor, the proportion of patients with information on HER2 positivity score (IHC status) available is provided and, on these patients, details about the HER2 positivity score (IHC status) (i.e., 0, 1+ or 2+) and about the origin (primitive tumor, advanced (locoregionally recurrent not amenable to surgery or metastatic) breast cancer or unknown) will also be described.

Levels of ER receptor, PgR receptor and Ki67 (%) will be analyzed both in continuous and in categorical terms classifying values as <20% or ≥20%.

Moreover, patients will be classified in the "Luminal A" or "Luminal B" category based on their **tumor type**. The following definition will be applied:

- Luminal A: Ki67<20%, ER positive, PgR≥20%, HER2 negative
  Or
  Ki67<20%, ER negative, PgR≥20%, HER2 negative;
- Luminal B: Ki67≥20% or PgR<20%;
- Unknown: otherwise

Information related to the **metastatic sites** collected in the "Diagnosis and extent of cancer - Metastatic sites" eCRF page will be summarized defining the following macro-categories:

- Bone: metastatic sites collected in the eCRF with codes
  - "22=Bone",
  - "24=Bone, cervical vertebrae"
  - "25=Bone, femur"
  - "26=Bone, lumbar vertebrae"
  - "27=Bone, other"
  - "28=Bone, pelvis"

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

- "29=Bone, sacrum"
- "30=Bone, scapulae and humeri"
- "31=Bone, sternum and ribs"
- "32=Bone, thoracic vertebrae"

Patients reporting one or more bone metastatic site without reference to any other metastatic site will be identified as "Bone only" and will also be considered as sub-category of bone sites.

- Visceral: metastatic sites collected in the eCRF with codes
  - Liver: "151=Liver"
  - Lung: "152=Lung", "203=Pleura" or "204=Pleural effusion (malignant)"
  - Liver or Lung: metastatic sites collected in the eCRF with codes classified as Lung or Liver defined as listed above.
  - Other visceral: "4=Adrenal", "5=Anal canal", "7=Appendix", "8=Ascites (malignant)", "20=Bile duct", "21=Bladder", "52=Cervix", "58=Colon", "81=Esophagus", "92=Gall bladder", "140=Kidney", "182=Omentum", "184=Ovary", "190=Pancreas", "199=Pericardial effusion (malignant)", "201=Peritoneum", "211=Prostate", "220=Rectum", "235=Small bowel", "239=Spleen", "241=Stomach", "270=Ureter" or "273=Uterus"

The sub-categories "Liver", "Lung", "Liver and Lung" and "Other visceral" will also be summarized.

- CNS: metastatic sites collected in the eCRF with codes:
  - "33=Brain"
  - "238=Spinal cord"
  - "155=Meninges"

- Lymph nodes: metastatic sites collected in the eCRF with codes:
  - "6=Anterior mediastinal lymph nodes"
  - "9=Axillary lymph nodes"
  - "36=Bronchopulmonary lymph nodes"
  - "50=Celiac lymph nodes"
  - "51=Cervical lymph nodes"
  - "59=Colonic lymph nodes"
  - "70=Deep inguinal lymph nodes"
  - "71=Deep jugular lymph nodes"
  - "72=Deep pulmonary lymph nodes"
  - "82=External iliac lymph nodes"
  - "91=Femoral lymph nodes"
  - "94=Gastric lymph nodes"
  - "95=Gastro-hepatic lymph nodes"
  - "112=Hepatic hilar lymph nodes"
  - "120=Internal iliac lymph nodes"
  - "130=Jugular lymph nodes"

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

- "156=Mesenteric lymph nodes"
- "180=Occipital lymph nodes"
- "192=Para-aortic lymph nodes"
- "193=Paracardiac lymph nodes"
- "194=Paraesophageal lymph nodes"
- "196=Parauterine lymph nodes"
- "197=Parotid lymph nodes"
- "206=Popliteal lymph nodes"
- "207=Posterior mediastinal lymph nodes"
- "208=Preauricular lymph nodes"
- "209=Pretracheal lymph nodes"
- "212=Pulmonary lymph nodes"
- "221=Retroauricular lymph nodes"
- "222=Retroperitoneal lymph nodes"
- "240=Splenic lymph nodes"
- "242=Subclavicular lymph nodes"
- "243=Submandibular lymph nodes"
- "244=Submental lymph nodes"
- "245=Subserosal lymph nodes"
- "246=Superficial inguinal lymph nodes"
- "247=Supraclavicular lymph nodes"
- "262=Thyroid lymph nodes"

Patients with metastatic site(s) coded as '998- Other' who reported further specifications containing the 'Node' term will be also included in this macro category.

- Skin: metastatic sites collected in the eCRF with code "231=Skin"
- Breast: metastatic sites collected in the eCRF with code "35=Breast". Patients with metastatic site(s) coded as '998- Other' who reported further specifications containing the 'Breast' term without reference to the 'Node' term will be also included in this macro category.
- Other: all metastatic sites collected in the eCRF with codes different from those mentioned above.

The number of organs of interest involved by metastases by patients will be described in continuous terms by means of the usual descriptive statistics. In the computation, metastatic sites belonging to the same organ will be counted once (i.e., different sites belonged to bone will be counted once as bone organ, as well as different sites belonging to lymph nodes will be counted once as lymph node organ). For this analysis the organs of interest considered are bone, liver, lung, CNS, lymphnodes, skin and breast. Metastatic sites classified as other (i.e., other visceral or other organs) are excluded from the computation of the number of organs of interest involved by metastases. A summary description in categorical terms providing the number of patients reporting one, two, three or more organs with by metastatic sites will also be performed. Within patients referring only one metastatic site, frequencies of subjects with metastatic site "bone", "Liver and Lung" and "neither bone nor liver or lung" will be described. Analogously, within patients referring two metastatic macro-categories,

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

frequencies of subjects with metastatic sites "Liver and lung included" and "Liver and lung not included" will be summarized also.

For all patients defined as non-de novo (see the definition of the non-de novo patients above in this section), the following variables will be calculated and summarized:

- **Disease free interval (DFI)**, defined as the time (in years) elapsed from the date of the last surgery (with typology different from biopsy) undergone by patients before study entry and the date of first recurrence/progression collected in the "Diagnosis and Extent of Cancer" eCRF page, plus one day. In case of negative values, the DFI will be forced to zero. Of note, DFI can be computed only on non-de novo patients performing any prior non-biopsy surgery.

  The disease-free interval will be described both in continuous terms by means of usual descriptive statistics and in categorical terms computing the frequencies of patients with DFI ≤5 years, >5 years to 7 years, >7 years.

- **Treatment-free interval (TFI)**, defined as the time (in months) elapsed from the end of the last adjuvant therapy to the date of first recurrence/progression collected in the "Diagnosis and Extent of Cancer" eCRF page, plus one day. In case of negative values, the TFI will be forced to zero. Of note, DFI can be computed only on non-de novo patients performing any prior adjuvant therapy.

  The treatment-free interval will be described both in continuous terms by means of usual descriptive statistics and in categorical terms computing the frequencies of patients with time ≤12 months, >12 to ≤24 months, >24 to ≤36 months, >36 to ≤48 months, >48 to ≤60 months, >60 months.

Absolute and relative percentage of patients with **measurable disease at screening** (i.e., patients with at least one target lesion according to the RECIST identification criteria) will be provided.

Frequency of patients performing **coagulation test at screening** will be described, and the international normalized ratio (INR) values summarized by means of the usual descriptive statistics.

Vital signs

Vital signs at screening will be described by means of the usual descriptive statistics. **Height** (cm), **weight** (kg), Body Mass Index (kg/m2), **body temperature** (°C), **pulse** (beats/min), **systolic and diastolic blood pressures** (mmHg) will be considered.

Body Mass Index at screening will be calculated dividing the last weight collected at screening/baseline before study drug administration by the square of height. BMI will be described both in continuous terms by means of usual descriptive statistics, and in categorical terms through frequencies of patients classifiable into the following categories:

- <18.5 kg/m2 underweight
- 18.5 kg/m2 - 24.9 kg/m2 normal weight
- 25.0 kg/m2 – 29.9 kg/m2 overweight

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- ≥30 kg/m2 obese

Medical history and Prior medications

Medical history will be described providing the absolute and relative frequencies of patients reporting any medical history/current medical condition/surgery/medical procedure. Medical histories/current medical conditions/surgeries/medical procedures will be summarized by System Organ Class (SOC), Preferred Term (PT). Further details (as ongoing condition and relative CTC grade) will be listed.

Prior medications (i.e., those medication started and ended before the start of the study treatment) will be, as first, summarized focusing on type of medication of major interest.

For all patients defined as non-de novo (see the definition of the non-de novo patients above in this section), a summary description of **prior adjuvant therapy** will be provided. More in detail, frequencies of patients who underwent endocrine therapy only (both in general and separately considering “Letrozole”, “Anastrozole”, “Exemestane” and “Tamoxifen” (including also “Tamoxifen citrate”) as Preferred Term), chemotherapy only or both endocrine therapy and chemotherapy (in general and considering the sub-categories “Chemotherapy but containing Letrozole”, “Chemotherapy but containing Anastrozole”, “Chemotherapy but containing Exemestane”, “Chemotherapy but containing Tamoxifen”) will be computed and tabulated. Endocrine therapies are identified as drugs coded with ATC code 2nd level='ENDOCRINE THERAPY'; Chemotherapies were defined as drugs coded with ATC code 2nd level='ANTINEOPLASTIC AGENTS'.

Frequencies of non-de novo recurrent patients taking or not **prior LHRH analog drugs** (i.e., Goserelin, Leuprolide) will be also summarized. LHRH analog drugs are defined as medication with ‘LHRH’ or ‘GOSERELIN’ or ‘LEUPROLIDE’ or ‘LEUPROLELIN’ in the Preferred Term and/or in the Low Level Term.

For all patients, the proportion of patients performing any prior adjuvant hormone -therapy (i.e., medication coded with ATC 2nd level= "ENDOCRINE THERAPY") will be provided together with the **duration of the adjuvant hormone-therapy** will be calculated as time elapsed from the start date of the hormonal adjuvant therapy to the end date plus one day. In case of more than one hormonal therapy, the duration will be calculated as time elapsed from the start of the first adjuvant hormone treatment to the end of the last one performed before study entry. The duration of adjuvant hormonal therapy will be described both in continuous term by means of the usual descriptive statistics and in categorical terms computing the frequencies of patients with time ≤5 years, >5 years to ≤7 years, >7 years.

The **treatment received for metastatic disease** (defined as any prior medication with therapeutic setting) will also be described in terms of frequencies of patients naïve (i.e., patients who never take medication in therapeutic setting) vs. taking max 28 days letrozole (i.e., patients who take ‘LETROZOLE’ in therapeutic setting for a maximum of 28 days) vs. taking plus than 28 days letrozole (i.e., patients who take ‘LETROZOLE’ in therapeutic setting for a more than 28 days) vs. taking max 28 days Anastrozole (i.e., patients who take ‘ANASTROZOLE’ in therapeutic setting for a maximum of 28 days) vs. taking plus than 28 days Anastrozole (i.e., patients who take ‘ANASTROZOLE’ in therapeutic setting for a more than 28 days).

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Moreover, a summary by setting (i.e., adjuvant, neoadjuvant, palliative, therapeutic, other), ATC code (2nd level) and Preferred term will be provided for collected **prior antineoplastic therapy – medications**, as well as the proportion of patients taking any prior antineoplastic medications. Further details as regimen number of each medication, start/end date of assumption, Reason for discontinuation of therapy, best response achieved, and date of progression will be provided in the Patient Data Listings document.

Frequencies of women reporting any prior antineoplastic radiotherapies will be calculated. Summary by setting (i.e., adjuvant, neoadjuvant, palliative, therapeutic, other) and location/site of **prior antineoplastic therapy – radiotherapies** will also be provided. Further details as other location/site specification and start/end date will be provided in the Patient Data Listings document.

Frequencies of patients reporting any prior antineoplastic surgeries will be computed, and a summary of **prior antineoplastic therapy – surgeries** by procedure (i.e., biopsy or other), SOC and PT will be provided. Further details as surgery description, date of surgery and residual disease will be provided in the Patient Data Listings document.

Other Prior medications could be collected in the "PRIOR AND CONCOMITANT MEDICATION" eCRF page, and they will be described by ATC code (2nd level class) and Preferred Term, presenting the number and percentage of patients taking at least one prior medication.

Extension phase

Background and demographic characteristics, vital signs, medical history and prior medications will be summarized descriptively for patients valid both for the FAS-EXT and for the BAS-EXT.

Demography & Disease and clinical characteristics

Demographic characteristics will be described by means of the same information presented for the Core phase of the study (i.e., age, race, and ethnicity). For patients entered the Extension phase, data collected during the ribociclib + letrozole phase will be summarized.

Disease and clinical characteristics will be described by means of the same information presented for the Core phase of the study, i.e., ECOG performance status at screening in both study phases, diagnosis and extent of cancer, hormone receptors status and levels of ER receptor, PgR receptor and Ki67, tumor type in the Core phase, metastatic sites in each study phase. More in details:

ECOG performance status at screening will be summarized with absolute and relative frequencies for each considered study phase.

Diagnosis and extent of cancer will be described providing the same information collected during the Core phase. Moreover, a summary of patients who re-evaluate the histological grade after the Screening of core study phase will be provided and, for these women, the re-evaluated histological grade will also be described.

Hormone receptors status during the Core phase will be described as previously detailed together with the levels of the considered receptor. The hormone receptor status during the Extension phase

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will also be described providing frequencies of patients who performed a re-evaluation of the receptor status after the screening of the Core study phase. For these women, a summary of HER2, Estrogen and Progesterone receptor status will be provided, as well as the description of ER and PgR receptors together considered. **Levels of ER receptor and PgR receptor** (%) will also be summarized by means of the usual descriptive statistics both as collected in the Core phase and considering the re-evaluation on women who re-evaluate the receptor status after the screening of the Core study phase.

The patients' tumor type in the Core phase will be described as previously reported.

Information related to the **metastatic sites** collected in the "Diagnosis and extent of cancer - Metastatic sites" eCRF page will be summarized both for the Core and the extension phases. For the Core phase will be provided the same description above detailed. For the extension phase, the following macro-categories will be defined:

- Bone: metastatic sites collected in the eCRF with codes
  - "22=Bone"

  Patients reporting one or more bone metastatic site without reference to any other metastatic site will be identified as "Bone only" and will also be considered as sub-category of bone sites.

- Visceral: metastatic sites collected in the eCRF with codes
  - Liver: "151=Liver"
  - Lung: "152=Lung", "203=Pleura" or "204=Pleural effusion (malignant)"
  - Liver or Lung: metastatic sites collected in the eCRF with codes classified as Lung or Liver defined as listed above.
  - Other visceral: "4=Adrenal", "5=Anal canal", "7=Appendix", "8=Ascites (malignant)", "20=Bile duct", "21=Bladder", "52=Cervix", "58=Colon", "81=Esophagus", "92=Gall bladder", "140=Kidney", "182=Omentum", "184=Ovary", "190=Pancreas", "199=Pericardial effusion (malignant)", "201=Peritoneum", "220=Rectum", "235=Small bowel", "239=Spleen", "241=Stomach", "270=Ureter" or "273=Uterus"

  The sub-categories "Liver", "Lung", "Liver and Lung" and "Other visceral" will also be summarized.

- Lymph nodes: metastatic sites collected in the eCRF with code "153=Lymph nodes". Patients with metastatic site(s) coded as '998- Other' who reported further specifications containing the 'Node' term will be also included in this macro category.

- CNS: metastatic sites collected in the eCRF with codes:
  - "33=Brain"
  - "238=Spinal cord"
  - "155=Meninges"

- Skin: metastatic sites collected in the eCRF with code "231=Skin"

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

- Breast: metastatic sites collected in the eCRF with code “35=Breast”. Patients with metastatic site(s) coded as '998- Other' who reported further specifications containing the 'Breast' term without reference to the 'Node' term will be also included in this macro category.
- Other: all metastatic sites collected in the eCRF with codes different from those mentioned above.

The number of organs of interest involved by metastases by patients by patients will be described in continuous terms by means of the usual descriptive statistics. In the computation, metastatic sites belonging to the same organ will be counted once (i.e., different sites belonged to bone will be counted once as bone organ, as well as different sites belonging to lymph nodes will be counted once as lymph node organ). For this analysis the organs of interest considered are bone, liver, lung, CNS, skin and breast. Metastatic sites classified as other (i.e., other visceral or other organs) are excluded from the computation of the number of organs of interest involved by metastases.

A summary description in categorical terms providing the number of patients reporting one, two, three or more organs with by metastatic sites will also be performed. Within patients referring only one metastatic site, frequencies of subjects with metastatic site “bone”, “Liver and Lung” and “neither bone nor liver or lung” will be described. Analogously, within patients referring two metastatic macro-categories, frequencies of subjects with metastatic sites “Liver and lung included” and “Liver and lung not included” will be summarized also.

Frequency of patients performing **coagulation test at screening** will be described for each study phase, and the international normalized ratio (INR), will be summarized by means of the usual descriptive statistics. Values collected of activated partial thromboplastin time (aPTT) and Partial thromboplastin time (PTT) in the Extension phase will be only listed since these parameters can be expressed in two different unit of measurements (i.e., ratio or second).

Vital signs

Vital signs at screening in Core phase will be reported as previously described. Vital signs collected during the Extension phase will be similarly described. **Weight** (kg), **body temperature** (°C), **pulse** (beats/min), **systolic and diastolic blood pressures** (mmHg) will be considered.

Body Mass Index at screening of the Extension phase will be calculated dividing the last weight collected at screening before study drug administration by the square of height collected in the Core phase. BMI will be described both in continuous terms by means of usual descriptive statistics, and in categorical terms through frequencies of patients classifiable into the following categories:

- <18.5 kg/m2 underweight
- 18.5 kg/m2 - 24.9 kg/m2 normal weight
- 25.0 kg/m2 – 29.9 kg/m2 overweight
- ≥30 kg/m2 obese

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

6.3. Efficacy Evaluation

The primary efficacy analysis will be performed on patients valid for the BAS and for the BAS-EXT for the Core and the Extension phases respectively.

The secondary efficacy analysis will also be performed on patients valid for BAS/BAS-EXT, and on FAS/FAS-EXT when specified in section 6.3.2 below.

6.3.1. Primary efficacy analysis

Core phase

Definition of primary endpoint

The primary objective of the Core phase of the study is to identify ctDNA alterations, how they evolve, and evaluate their possible association with clinical outcome in the ribociclib + letrozole phase of treatment. Therefore, the primary endpoint of the present interim analysis is based on the analysis of ctDNA dynamic and its association with clinical outcome.

Patients' blood samples (whole blood and serum) are collected at baseline, at cycle 1-day 15, cycle 2-day 1, at first imaging evaluation, and at EOT. The valid blood samples are used to perform multiple gene assessments of ctDNA by means of the Next Generation Sequencing (NGS) analysis conducted by Eurofins GENOMA Group S.r.l. Two panel are used to detect genes mutations, the Oncomine Pan-Cancer (Thermofisher) panel and the NGS BioItaLEE Custom panel. Genes assessed by each panel are detailed in table 6.3.1-1, as well as the type of mutation (i.e., hotspot mutations vs. CNV amplifications) identifiable by the panels. Since many analyses have been performed to explore differences and similarities between the two panels (refer to section 6.6), the present analysis will be focused on the results of the **hotspot mutational analysis** obtained using the NGS BioItaLEE Custom panel. Therefore, 39 genes will be considered.

Table 6.3.1-1 – Genes by panel and type of analysis

Gene	Oncomine Pan-Cancer (Thermofisher) panel		BioItaLEE Custom panel
	Hotspot Mutational analysis	Amplification (CNV) analysis	Hotspot Mutational analysis
[redacted]			

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Gene	Oncomine Pan-Cancer (Thermofisher) panel		BioItaLEE Custom panel
	Hotspot Mutational analysis	Amplification (CNV) analysis	Hotspot Mutational analysis
[redacted]			

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Gene	Oncomine Pan-Cancer (Thermofisher) panel		BioItaLEE Custom panel
	Hotspot Mutational analysis	Amplification (CNV) analysis	Hotspot Mutational analysis
[redacted]			

For the genes analyzed for hotspot mutations, the mutated variant ID (*Amino_Acid_change* variable) and the relative calculated molecular frequency (*mol_freq_perc_calcolata* variable, i.e., the VAF) are recorded.

For each patient reporting any hotspot mutation, the **target mutation** will be identified. Target mutation is the hotspot mutation (in terms of gene and variant ID combination) detected at screening with the highest molecular frequency[redacted]. The following assumptions will be done:

- Only the hotpot mutations detected at screening will be considered.
- For post-screening timepoints where a mutation is not detected, its molecular frequency will be set to 0% if the liquid biopsy evaluation is done, missing otherwise.
- [redacted]

Focusing on the mutational status, patients will also be **classified** as follows:

Screening

- Wild Type

  Patients without hotspot mutations (target or not) detected at screening. [redacted]

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

- Mutated

  Patients with a target mutation detected at screening.

Mutational early dynamic change (i.e., considering C1D15)

- Early confirmed Wild Type

  Wild Type patients [redacted] at screening without hotspot mutations detected at C1D15.

- New Early mutated

  Wild Type patients [redacted] at screening who develop any new hotspot mutation at C1D15.

- Early cleared

  Mutated patients with 100% decrease in target mutation VAF at C1D15.

- Early persistent

  Mutated patients without 100% decrease in target mutation VAF at C1D15.

Mutational dynamic change (i.e., considering C1D15 and C2D1 together)

- Persistent Wild Type

  Wild Type patients [redacted] at screening without hotspot mutations detected both at C1D15 and C2D1.

- Mutated but cleared at C1D15 or C2D1

  Mutated patients with 100% decrease in target mutation VAF at C1D15 or at C2D1.

- Persistent mutated

  Mutated patients without 100% decrease in target mutation VAF both at C1D15 and C2D1.

Of note, among patients with valid sample at screening and at C1D15 and at C2D1, there could be also patients 'New mutated' that will be Wild Type patients [redacted] at screening with hotspot mutations detected at C1D15 or C2D1. Since this groups of patients could be related to false negative results at screening and/or at C1D15, making it difficult to offer an unbiased clinical interpretation, they will be excluded from analysis.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Complete mutational dynamic change (i.e., considering C1D15, C2D1 and FI)

- Persistent Wild Type

  Wild Type patients [redacted] at screening without hotspot mutations detected at any subsequent assessment (i.e., C1D15, C2D1, FI).

- Confirmed cleared

  Mutated patients with 100% decrease in target mutation VAF at C1D15 or at C2D1 that is also observed at FI (i.e., 100% decrease in target mutation VAF at FI).

- Unconfirmed cleared

  Mutated patient that cleared or at C1D15 or at C2D1 (i.e., with 100% decrease in target mutation VAF at C1D15 or at C2D1) that were not still cleared at FI (i.e., without 100% decrease in target mutation VAF at FI).

- Late cleared

  Mutated patients without 100% decrease in target mutation VAF at C1D15 and at C2D1 but with 100% decrease in target mutation VAF at FI.

- New mutated

  Wild Type patients [redacted] at screening with hotspot mutations detected at C1D15 or C2D1.

- Late mutated

  Wild Type patients [redacted] at screening without hotspot mutations detected at C1D15 and C2D1 but with hotspot mutations detected at FI.

- Confirmed mutated

  Mutated patients without 100% decrease in target mutation VAF at any subsequent assessment (i.e., C1D15, C2D1, FI).

Patients' **PFS**, the clinical outcome, will be calculated (in months) as:

PFS (months)= (date of PFS event/censoring – date of C1D1 + 1 day)/30.4375

Censoring rules to be applied are described in Section 4.2 of the present document.

Analysis methodology

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

A summary description of patients' **liquid biopsy sample status** by scheduled timepoint will be provided to summarize frequency of patients with sample collected/compliant/valid at each considered scheduled timepoint. More in detail:

- Sample collected/not collected will be evaluated on patients valid for BAS at each considered timepoint (i.e., baseline, C1D15, C2D1, First Imaging, EoT stratified by EOT due to progression of disease and EOT due to other reason).
- For patients with biopsy collected, the number of subjects with compliant/non-compliant samples (due to any reason) at each timepoint will be provided. Biopsy is defined compliant when the "CampioneIdoneo" variable of data provided by Eurofins GENOMA Group S.r.l. is equal to 1; biopsy is considered not compliant when the "CampioneIdoneo" variable is equal to 2.
- For patients with compliant biopsy, the number of subjects with biopsy valid/not valid for the NGS analysis at each considered timepoint will be summarized. A sample is considered valid for the NGS analysis if the "Locus" variable of data provided by Eurofins GENOMA Group S.r.l. is different from "NV"; a sample is considered not valid for the NGS analysis if the "Locus" variable is equal to "NV".

A summary description of number of patients reporting at least one **hotspot mutation** overall and on each of the 39 considered genes belonging to the BioItaLEE Custom panel will be provided by scheduled timepoint. Patients with more than one mutated allele on the same gene will be counted once.

The number of hotspot mutations observed by patient at each considered timepoint will be calculated and summarized in categorical terms (i.e., frequencies of patients reporting no hotspot mutation, one mutation, two mutations or three mutations or more). All the mutations interesting either the same gene (i.e., different variants on the same gene) or different genes (i.e., different variants in different genes) will be considered in the computation.

Genes and variants interested by hotspot mutations will be listed.

Frequencies of patients reporting a **target mutation** will be provided, as well as a summary of genes interested by the target mutation. A description of the patients' target mutation VAF over timepoints will also be provided together with the change vs. screening. A box plot will be drawn to graphically represent target mutation VAF over scheduled timepoints.

Summary description of **patients' distribution in categories** defined on screening mutational status, on C1D15 early dynamic change, on Mutational dynamic change based on C1D15 and C2D1 and on Complete mutational dynamic change based on C1D15, C2D1 and FI will be provided.

The **PFS** probability will be estimated using the Kaplan-Meier method considering screening mutational status (wild type - mutated), C1D15 mutational early dynamic change (Early confirmed Wild Type - New Early mutated - Early cleared - Early persistent), Mutational dynamic change based on C1D15 and C2D1 (Persistent Wild Type – Mutated but cleared at C1D15 or C2D1 – Persistent mutated) and on Complete mutational dynamic change based on

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

C1D15, C2D1 and FI (Persistent Wild Type – Late Mutated – New Mutated – Persistent Mutated – Confirmed cleared) categories separately. PFS median time will be estimated along with 95% confidence interval only if enough responses are observed. Kaplan-Meier curves will be plotted, and Log rank test will be performed to descriptively compare curves.

Cox models for PFS will be also fitted including screening mutational status, C1D15 mutational early dynamic change, Mutational dynamic change based on C1D15 and C2D1 and on Complete mutational dynamic change based on C1D15, C2D1 and FI respectively as independent variable. The following clinical baseline variables will be added as adjustment:

- Patients' status (de novo vs. recurrent).
- Tumor type (Luminal A vs. Luminal B).
- Visceral metastases (presence vs. absence).
- Number of organs involved by metastases (0, 1, 2 vs. 3 or more).

Focusing on samples collected at EOT only for patients who discontinue the Core phase for the study due to progression of disease, patients' distribution according to liquid biopsy results will be described based on the following categories:

- Wild type
- Positive only for target mutation (i.e., detection of VAF > LOD on target hotspot mutation only at EOT)
- Positive only for new mutation (i.e., detection of VAF > LOD for any gene different from target hotspot mutation at EOT)
- Positive for target and other mutation (i.e., detection of VAF > LOD both for any gene different from target and for target hotspot mutation at EOT)

Sensitivity of primary analysis

No sensitivity analysis is foreseen for this endpoint.

Extension phase

Definition of primary endpoint

The primary objective of the Extension phase of the study is to identify ctDNA alterations, how they evolve, and evaluate their possible association with clinical outcome in the alpelisib + fulvestrant phase of treatment.

Patients' individual history will be considered together with the results of the liquid biopsy samples and graphically represented.

Analysis methodology

Patients' individual history will be graphically represented by means of a Swimmer plot. The graph will include one bar for each patient showing the length of individual treatment duration. Moreover, indicators for the start and end of each achieved response, classified by complete or partial response, will be displayed. Different symbols at the end of bars will

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provide information about the reason for the treatment discontinuation (death, progression of disease or other causes) and the death, if occurred.

Each patient will also be classified on the basis of her exposure to ribociclib/letrozolo taken during the Core phase: greater or equal to 24 months or lower than 24 months.

A similar swimmer plot will be provided considering the mutational status as classification variable according to these categories:

- 'PIK3CA Mutated with confirmed clearance during extension': patient with PIK3CA mutated at screening that cleared any time during extension and remain cleared at last available evaluation.
- 'PIK3CA Mutated with unconfirmed clearance during extension': patient with PIK3CA mutated at screening that cleared any time during extension but then are not cleared at last available evaluation.
- 'PIK3CA Mutated without confirmed clearance during extension': patient with PIK3CA mutated at screening that remained mutated during extension.
- 'Wild type for PIK3CA at screening that shows PIK3CA mutation during extension'
- 'Wild type for PIK3CA at screening that remain wild type during extension'
- 'No dynamic information available': patient without any liquid biopsy results after the screening during the extension phase

The mutated variant of PIK3CA will be also displayed.

6.3.2. Secondary efficacy analysis

6.3.2.1. TK1 serum levels and association with clinical outcome

Patients' TK1 serum levels are collected during the Core phase only. Serum samples are analyzed by Unità di Ricerca Traslazionale "Sandro Pitigliani" - Nuovo Ospedale di Prato.

Definition

TK1 is a cellular enzyme involved in DNA precursor synthesis, and its activity has been used as a proliferation marker for monitoring malignant diseases. It is analyzed on serum by chemiluminescence immunoassay. According to the study protocol, it is collected at screening, C1D1, C1D15, C2D1, first imaging evaluation and at end of treatment timepoints.

In the present analysis, the TK1 activity over time as blood marker of proliferation and its association with clinical outcome will be evaluated.

Patients will be classified in the following **categories** on the basis of their TK1 serum levels:

Screening serum level

- TK1 low

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TK1 serum level equal to or lower than the median value observed at screening on patients valid for BAS with valid serum sample.

- TK1 high

  TK1 serum level at screening greater than the median level observed considering all patients valid for the Biomarker Analysis Set with valid serum sample at screening.

C1D15 TK1 early dynamic change

- TK1 below LOD

  TK1 serum level below the detection limit of 20Du/L at C1D15

- TK1 above LOD

  TK1 serum level equal or above the detection limit of 20 <du/L at C1D15

Dynamic change (i.e., considering C1D15 and C2D1 together)

- TK1 inhibited

  TK1 serum level below the detection limit at C1D15 and at C2D1

- TK1 rebounded

  TK1 serum level below the detection limit at C1D15 but above at C2D1

- TK1 insufficiently inhibited

  TK1 serum level above the detection limit at C1D15

Complete TK1 dynamic change (i.e., considering C1D15, C2D1 and FI)

- Inhibited confirmed inhibited

  TK1 serum level below the detection limit at C1D15 and at C2D1 and also at FI.

- Late inhibited from rebound

  TK1 serum level below the detection limit at C1D15 but above at C2D1 and then below the detection limit at FI.

- Rebound confirmed rebound

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TK1 serum level below the detection limit at C1D15 but above at C2D1 that remain above the detection limit at FI.

- Late inhibited from insufficiently inhibited

  TK1 serum level above the detection limit at C1D15 and then below the detection limit at FI.

- Late rebound from inhibited

  TK1 serum level below the detection limit at C1D15 and at C2D1 but above at FI.

- Persistent insufficiently inhibited

  TK1 serum level above the detection limit at C1D15 that remain above the detection limit at FI.

Analysis methodology

A summary description of patients' serum samples status by scheduled timepoint will be provided to summarize frequency of patients with sample collected/valid at each considered scheduled timepoint. More in detail:

- Sample collected/not collected will be evaluated on patients valid for BAS at each considered timepoint (i.e., baseline, C1D15, C2D2, First Imaging, EoT stratified by EOT due to progression of disease and EOT due to other reason).
- For patients with biopsy collected, the number of subjects with valid/not valid samples (due to any reason) at each timepoint will be provided.

A summary description of patients' **TK1 serum level** over time will be provided together with percentage change vs. screening by scheduled timepoint. Since the detection limit for TK1 corresponds to 20 Du/L, TK1 levels recorded as <20 Du/L will be considered as 19 Du/L. A box plot representing the TK1 Serum level distribution over scheduled timepoints will be provided. The log10 of TK1 level will be plotted on Y axe in order to improve reading.

Summary description of patients' **distribution in TK1 defined categories** will be provided.

The **PFS** probability will be estimated using the Kaplan-Meier method considering screening TK1 status (low level – high level), C1D15 TK1 early dynamic change (TK1 below LOD – TK1 above LOD), TK1 dynamic change (TK1 inhibited – TK1 rebounded – TK1 insufficiently inhibited) and Complete TK1 dynamic change (Inhibited confirmed inhibited – Late inhibited from rebound – Rebound confirmed rebound – Late inhibited from insufficiently inhibited – Late rebound from inhibited – Persistent insufficiently inhibited) categories separately. PFS median time will be estimated along with 95% confidence interval only if enough responses are observed. Kaplan-Meier curves will be plotted, and Log rank test will be performed to descriptively compare curves.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Cox models for PFS will be also fitted including screening TK1 status, C1D15 TK1 early dynamic change, TK1 dynamic change and Complete TK1 dynamic change respectively as independent variable. The following clinical baseline variables will be added as adjustment:

- Patients' status (de novo vs. recurrent).
- Tumor type (Luminal A vs. Luminal B).
- Visceral metastases (presence vs. absence).
- Number of organs involved by metastases (0, 1, 2 vs. 3 or more).

Moreover, TK1 dynamic change categories will be analyzed within Mutational dynamic change based on C1D15 and C2D1 categories. Firstly, the PFS probability will be estimated using the Kaplan-Meier method considering TK1 dynamic change (TK1 inhibited – TK1 rebounded – TK1 insufficiently inhibited) in each Mutational dynamic change based on C1D15 and C2D1 (Persistent Wild Type – Mutated but cleared at C1D15 or C2D1 – Persistent mutated). Cox models for PFS will be fitted including TK1 dynamic change and the clinical baseline variables as adjustment (i.e., patients' status tumor type, visceral metastases, number of organs involved by metastases) in each Mutational dynamic change based on C1D15 and C2D1 (Persistent Wild Type – Mutated but cleared atC1D15 or C2D1 – Persistent mutated).

Sensitivity of secondary analysis

Not applicable.

6.3.2.2. ctDNA alterations in long responders and early progressors

Core phase

Definition

The present secondary endpoint will be focused on two defined subgroups of patients: long responders and early progressors.

Long responders are subjects reporting a Time to Progression >25 months.

Early progressors are subjects who report a documented progression of disease at the tumor assessment at the first imaging evaluation performed up to 112 days after C1D1.

Analysis methodology

The same descriptions provided for the primary analysis will be repeated for long responders and early progressors. Baseline, C1D15, C2D1 and First imaging are the timepoints that will be considered to clinically evaluate any difference between the two considered subgroups. No formal tests will be provided to evaluate any difference from a statistical point of view.

A summary description of number of patients reporting at least one hotspot mutation overall and on each of the 39 considered genes belonging to the BioItaLEE Custom panel will be

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provided by subgroup and scheduled timepoint. Patients with more than one mutated allele on the same gene will be counted once.

The number of hotspot mutations observed by patient at each considered timepoint will be calculated and summarized in categorical terms. All the mutations interesting either the same gene (i.e., different variants on the same gene) or different genes (i.e., different variants in different genes) will be considered in the computation.

Frequencies of patients reporting a target mutation will be provided, as well as a summary of genes interested by the target mutation. A description of the patients' target mutation VAF over timepoints will also be provided together with the change vs. screening. A box plot will be drawn to graphically represent target mutation VAF over scheduled timepoints.

Summary description of patients' distribution in categories defined on screening mutational status, on C1D15 early dynamic change, on Mutational dynamic change based on C1D15 and C2D1 and on Complete mutational dynamic change based on C1D15, C2D1 and FI will be provided.

Sensitivity of secondary analysis

Not applicable.

6.3.2.3. Mutational alterations in screening ctDNA and tissue sample in de novo and recurrent patients

Core phase

Definition

For the present secondary endpoint, patients will be classified on the basis of their disease status.

De novo patients are newly diagnosed subjects (refer to section 6.2 for further details on their identification).

Recurrent patients are subjects entered in the present study after a previous diagnosis of breast cancer.

Patients' **tissue** sample is collected at baseline and at the disease progression and it is analyzed by Eurofins GENOMA Group S.r.l. The NGS BioItaLEE Custom panel is used to detect hotspot mutations on the 39 genes detailed in Table 6.3.1-1.

Analysis methodology

A summary description of number of patients reporting valid screening samples of liquid biopsy and tissue will be provided both for de novo and for recurrent patients.

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Frequency of patients reporting at least one hotspot mutation overall and considering each gene belonged to the BioItaLEE Custom panel at screening will be provided by disease status. Patients with more than one mutated allele on the same gene will be counted once.

The number of hotspot mutations observed by patient at screening will be calculated by disease status and biological sample (i.e., liquid biopsy and tissue sample) and summarized in categorical terms (i.e., no hotspot mutation, one mutation, two mutations or three mutations or more). All the mutations interesting either the same gene (i.e., different variants on the same gene) or different genes (i.e., different variants in different genes) will be considered in the computation.

Sensitivity of secondary analysis

Not applicable.

6.3.2.4. Agreement between liquid biopsies and tissue samples

Core phase

Definition

As mentioned in previous section, patients' tissue sample is collected at baseline and at the disease progression, and it is analyzed by Eurofins GENOMA Group S.r.l. The NGS BioItaLEE Custom panel is used to detect hotspot mutations on the 39 genes detailed in Table 6.3.1-1.

Patients' baseline tissue samples are classified according to:

- Tumor tissue origin, i.e., metastatic or primitive tissue.
- Tumor tissue collection time, i.e., recent tissue or archival tissue. Recent sample is defined as a tissue sample collected within 6 months before C1D1 date; archival sample as a tissue sample collected more than 6 months before C1D1 date.

Analysis methodology

A summary description of patients' **tissue sample status** over scheduled timepoints will be provided to summarize frequency of patients with sample collected/suitable/valid. EOT timepoint will be presented only for patients discontinued the core treatment due to disease progression or deceased due to study indication. More in detail:

- Sample collected/not collected will be evaluated on patients valid for BAS.
- For patients with tissue collected at baseline, the number of subjects with sample suitable/not suitable for the pre-analytic analysis will be provided. A sample is considered valid for the pre-analytic analysis if the "CampioneIdoneo" variable of data provided by Eurofins GENOMA Group S.r.l. is equal to 1; sample is considered not valid for the pre-analytic analysis when the "CampioneIdoneo" variable is equal to 2.
- For patients with collected pre-analytically valid tissue sample, the number of subjects with sample valid/not valid for the NGS analysis will be provided. A sample is considered valid for the NGS analysis if the "Locus " variable of data provided by

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Eurofins GENOMA Group S.r.l. is different from "NV"; on the contrary, a sample is considered not valid for the NGS analysis when the "Locus" variable is equal to "NV".

Focusing on valid baseline tissue samples, a **summary** of patients' distribution **by tumor tissue origin and tumor tissue time of collection** will be provided. The following formula will be implemented to distinguish recent from archival tissue samples:

Time from tissue collection (months) = (date of C1D1 – date of tissue sample collection)/30.4375.

A tissue sample will be considered recent for time less than or equal to 6 months; archival for times greater than 6. In case of missing date of tissue sample collection, the information collected in the eCRF will be taken into account.

For patients with both liquid biopsy and tissue sample valid at screening, the results of the NGS analysis performed on both biological screening samples will be compared. For each gene belonging to the BioItaLEE custom panel, the following information will be provided:

- 2x2 contingency table reporting frequencies of patients for whom mutation is detected or not considering each sample.
- McNemar test p-value.
- Cohen's Kappa together with 95% CI.

The McNemar's test will be performed to test the hypothesis that the proportion of subjects with a certain response (i.e., with hotspot mutation(s) on each considered gene) is equivalent between the two NGS analyses (i.e., the one on liquid biopsy and the one on tissue sample). The McNemar's test focuses only on the discordant pairs (i.e., referring to an ideal 2x2 contingency table, the off-diagonal pairs for which the responses do not agree), ignoring the concordant pairs which do not give any information about the differences between the responses. In case of small numerousness (n lower than or equal to 20 subjects), the exact McNemar's test will be performed to replace the normal approximation to the binomial distribution of the McNemar's test with the exact binomial distribution.

The Cohen's Kappa statistic will also be computed, together with its 95% CI, in order to determine the level of agreement between these responses. It provides a global assessment of the agreement between the results obtained on liquid biopsy and on tissue sample. It is expressed as the normed difference between the rate of agreement that is actually observed and the rate of agreement that would be expected purely by chance. Cohen's Kappa values range between 0 (when the two methods agree only as often as they would by chance) to 1 (if the two methods are fully concordant). Negative values of Cohen's kappa are possible and would indicate that the two methods agree even less often than they would by chance, i.e., that they tended to make opposite judgments (corresponding to extreme negative value of -1). The interpretation of this statistic is arbitrary since there is no formal scale. However, Altman [1] suggested to categorize values of Cohen's Kappa as shown in the following Table 6.3.2.5-1.

Table 6.3.2.5-1- – Categorization of values of Cohen's kappa

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Value of K	Quality of agreement
<0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.0	Very good

Moreover, the **overall agreement** between baseline liquid biopsy results and tissue samples results will be calculated summing the relative frequencies calculated by each gene belonging to the BioItaLEE Custom panel. McNemar's test and Cohen's Kappa are applied on the total numbers of evaluations (hotspot-mutated or non-mutated) assuming that they are independent units. Therefore, the total number of evaluations will be defined by the number of BAS patients with both valid baseline liquid biopsy and tissue sample multiplied by the 39 considered genes.

The same analyses performed on baseline samples will be repeated considering the results obtained at the disease progression. Summary description and agreement by gene will be repeated considering the patients who discontinued the core phase of the study due to progressive disease with both valid liquid biopsy and tissue sample, as well as the overall agreement at the EOT timepoint.

Sensitivity of secondary analysis

Not applicable.

6.3.2.5. Clinical efficacy of study treatment

Core phase

Definition

The clinical efficacy of study treatment is evaluated considering ORR, CBR and TTP (refer to definition reported in section 4.2 of the present document).

The analysis of the present secondary endpoint will be performed on patients valid for BAS and on patients valid for FAS.

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Analysis methodology

Tumor responses reported by patients at each performed imaging evaluation will be summarized by scheduled timepoint, as well as the frequencies of patients performing each tumor assessment.

The **Best Overall Response** achieved by patients will be summarized providing frequency of subjects with CR, PR, SD and PD on patients performing at least one post-baseline imaging evaluation.

Patients' **ORR** and **CBR** will be described in terms of frequency of patients achieving/reporting the condition of interest. 95% confidence intervals will be computed using Clopper and Pearson (1934) exact method.

The **TTP** event-free probability will be estimated using the Kaplan-Meier method and the median time will be presented along with 95% confidence interval only if enough responses are observed. The results will also be plotted graphically. Censoring rules to be applied in TTP calculation are described in Section 4.2 of the present document.

Sensitivity of secondary analysis

Not applicable.

Extension phase

Definition

The clinical efficacy of study treatment is evaluated considering ORR, CBR, TTP and PFS2 (refer to definition reported in section 4.2 of the present document).

The analysis of the present secondary endpoint will be performed on patients valid for BAS-EXT and on patients valid for FAS-EXT.

Analysis methodology

The same analyses described for the Core phase for tumor responses, best overall response, ORR, CBR and TTP will be repeated for the Extension phase.

The **PFS2** probability will be estimated using the Kaplan-Meier method and the median time will be presented along with 95% confidence interval only if enough responses are observed. The results will also be plotted graphically by means of Kaplan-Meier curve. Censoring rules to be applied in PFS2 calculation are described in Section 4.2 of the present document.

Sensitivity of secondary analysis

Not applicable.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

[redacted]	**Statistical Analysis Plan**
	Sponsor: Novartis **Protocol number: CLEE011AIT01**

[redacted]

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[redacted]	**Statistical Analysis Plan**
	Sponsor: Novartis **Protocol number: CLEE011AIT01**

[redacted]

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

[redacted]

6.3.4. Measurement of Treatment Compliance

Not applicable for the present study. Duration of study treatment exposure, cumulative dose, dose intensity, relative dose intensity and details about dose adjustments are provided in following section 6.4.1.

6.4. Safety Evaluation

Safety evaluation will be performed on SAF and SAF-EXT populations for the Core and the Extension phases respectively.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

6.4.1. Extent of Exposure

Extent of Exposure will be calculated separately for Core and Extension phases.

Core phase

The extent of exposure will be evaluated by means of the variables defined as follow.

Duration of exposure to study treatment

For all patients who take at least one dose of any of the components of the study treatment (i.e., ribociclib and/or letrozole), the duration of the exposure to the study treatment is calculated as:

Duration of exposure (days) = Date of last administration of study treatment – Date of first administration of study treatment + 1 day.

The duration of exposure to study treatment includes the periods of temporary interruption of the study treatment for any reason.

The duration of the exposure to study treatment (here represented as *d*) will also be categorized into time intervals as follows:

- $d \leq 12$ months
- 12 months $< d \leq 24$ months
- 24 months $< d \leq 36$ months
- 36 months $< d \leq 48$ months
- $d > 48$ months

Absolute and relative frequencies will be presented for each interval.

Of note, the last administration of study treatment for some patients will not refer to a permanent discontinuation of study treatment but to a study close out decided by Sponsor for rationale of study protocol amendment number 4.

Duration of exposure to each study treatment component

Similarly, the duration of exposure to ribociclib/letrozole will be defined as:

Duration of exposure to ribociclib (days) = Date of last administration of ribociclib – Date of first administration of ribociclib + 1 day.

Duration of exposure to letrozole (days) = Date of last administration of letrozole – Date of first administration of letrozole + 1 day.

Adjusted duration of exposure to ribociclib

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

The adjusted duration of exposure (expressed in days) for ribociclib is the number of ribociclib dosing days a patient would be expected to have received per protocol, given their duration of exposure to study treatment as defined above. Since ribociclib follows a 3-weeks-on/1-week-off schedule, the adjusted duration of exposure to ribociclib is the duration of exposure to study treatment minus the planned off days for ribociclib/placebo. Therefore:

Adjusted duration of exposure to ribociclib (days)= 21 x (nr. of completed 28 days cycles) + min(21, duration of last incomplete cycle).

For example:

if the duration of exposure to study treatment is 66 (corresponding thus to two cycles and 10 days), then the adjusted duration of exposure to ribociclib is 21*2+10=52. If the duration of exposure to study treatment is 108 days (corresponding to three cycles and 24 days), then the adjusted duration of exposure is 21*3+21=84.

Specifically, let D1 represents the duration of exposure to study treatment (and not the duration of the study treatment component) as defined above. Then the adjusted duration of exposure is defined as D=21*[D1/28] + min (21, D1-28*[D1/28]), where [x] stands for the integer part of x.

The adjusted duration of exposure includes the periods of temporary interruption.

Cumulative dose

The cumulative dose is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment component separately. For patients who do not receive any drug the cumulative dose will be set to zero.

Average daily dose

The average daily dose is computed as follows:

Average daily dose (mg/die) = Cumulative dose (mg) / Total number of treated days

Where total number of treated days is computed as the sum of days elapsed between the start and the end date of treatment of each dose different from zero collected in the DAR eCRF page.

Dose Intensity (DI)

Dose intensity for patients with non-zero duration of exposure is defined as follows:

DI (mg/die) = Cumulative dose (mg) / Duration of exposure (die).

For patients who do not receive any drug, the DI is set to zero.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

DI will be calculated separately for each of the study treatment components using the duration of the treatment component exposure. The DI calculation for ribociclib will use the adjusted duration of exposure for ribociclib to consider the 'off' days when no ribociclib is expected to be administered.

Planned Dose Intensity (PDI)

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as per protocol in the same dose unit and unit of time as that of the Dose Intensity. The planned dose intensity for ribociclib is 600 mg/die and the planned dose intensity for Letrozole is 2.5 mg/die.

Relative Dose Intensity (RDI)

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/die) / PDI (mg/die).

Duration of the exposure to the study treatment, duration of the exposure to each component of the study treatment, cumulative dose and average daily dose will be summarized by means of the usual descriptive statistics, as well as DI and RDI for each component of the study treatment.

Dose changes: reductions, interruptions

The proportion of patients who have any dose change, i.e., any dose reduction (for ribociclib only) or dose interruption will be summarized separately for each of the study treatment component and for the study treatment.

'Dose changed', 'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration eCRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively. Only dose change is collected in the eCRF, number of reductions will be derived programmatically based on the change and the direction of the change.

The following definitions are foreseen:

Reduction (for ribociclib only): A reduction is defined as a decrease in ribociclib dose from the protocol planned dose or a decrease from the previous non-zero dose during the dosing period, even if this decrease has been directly preceded by an interruption. For example, in the sequence 600mg – 0mg – 400mg, the 400mg dose will be counted as a reduction. In this study, letrozole dose reduction is not allowed. Due to dosing error if a patient took a dose during the dosing break with a dose that is lower than the previous dose, this will not be considered as dose reduction. For example, a patient took 600 mg from day 1-21, and on day 22-28, the patient accidently took 200 mg per day which is supposed to be a dosing break. The patient resumed 600 mg dosing on day 29. This will not be considered a dosing reduction.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Frequency of patients reporting at least one dose reduction for ribociclib will be provided, as well as the proportion of patients with no/one/two ribociclib reductions.

Time to first ribociclib reduction (TTFRR) is defined, for subjects reporting any reduction, as time elapsed from the ribociclib start date to the date of the first reported reduction. It will be calculated as follows:

TTFRR (days)= (date of first observed ribociclib reduction– ribociclib start date + 1 day)

Time to second ribociclib reduction (TTSRR) is defined, for patients who performed two ribociclib reductions, as time elapsed from the first ribociclib reduction to the second reported reduction. It will be calculated as follows:

TTSRR (days)= (date of second observed ribociclib reduction – date of first observed ribociclib reduction + 1 day)

Summary description of time to first and time to second ribociclib reduction will be provided by means of the usual descriptive statistics.

Interruption: An interruption is defined as a 0 mg dose given on one or more days during the period when a patient is not on the "off" part of a treatment cycle, after which >0 mg dose resumes.

Frequency of patients referring at least one interruption will be summarized separately for ribociclib and letrozole, and "overall" for study treatment.

Summary of number of temporary interruptions by patient and of number of temporary interruptions by patient for subjects reporting at least one interruption will be provided considering the usual descriptive statistics. Frequency of patients reporting none/one-two/three-five/more than five temporary interruptions will also be provided.

Extension phase

The extent of exposure for the Extension phase will be evaluated by means of the variables defined as follow.

Duration of exposure to study treatment

For all patients who take at least one dose of any of the components of the study treatment (i.e., alpelisib and/or fulvestrant), the duration of the exposure to the study treatment is calculated as:

Duration of exposure (days) = Date of last administration of study treatment – Date of first administration of study treatment + 1 day.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

The duration of exposure to study treatment includes the periods of temporary interruption of the study treatment for any reason.

The duration of the exposure to study treatment (here represented as *d*) will also be categorized into time intervals as follows:

- *d* ≤12 months
- 12 months < *d* ≤ 24 months
- 24 months < *d* ≤ 36 months
- 36 months < *d* ≤ 48 months
- *d* >48 months

absolute and relative frequencies will be presented for each interval.

Of note, the last administration of study treatment for some patients will not refer to a permanent discontinuation of study treatment but to a study close out decided by Sponsor for rationale of study protocol amendment number 4.

Duration of exposure to each study treatment component

Similarly, the duration of exposure to alpelisib/fulvestrant will be defined as:

Duration of exposure to alpelisib (days) = Date of last administration of alpelisib – Date of first administration of alpelisib + 1 day.

Duration of exposure to fulvestrant (days) = Date of last administration of fulvestrant – Date of first administration of fulvestrant + 1 day.

Cumulative dose

The actual cumulative dose is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment component separately. For patients who do not receive any drug the cumulative dose will be set to zero.

Average daily dose

The average daily dose is computed as follows:

Average daily dose (mg/die) = Cumulative dose (mg) / Total number of treated days

Where total number of treated days is computed as the sum of days elapsed between the start and the end date of treatment of each dose different from zero collected in the DAR eCRF page.

Dose Intensity (DI)

Dose intensity for patients with non-zero duration of exposure is defined as follows:

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

DI (mg/die) = Cumulative dose (mg) / Duration of exposure (die).

For patients who do not receive any drug, the DI is set to zero.

DI will be calculated only for alpelisib treatment using the duration of the alpelisib exposure.

Planned Dose Intensity (PDI)

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as per protocol in the same dose unit and unit of time as that of the Dose Intensity. The planned dose intensity for alpelisib is 300 mg/die.

Relative Dose Intensity (RDI)

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/die) / PDI (mg/die).

Duration of the exposure to the study treatment, duration of the exposure to each component of the study treatment, cumulative dose and average daily dose will be summarized by means of the usual descriptive statistics. In addition, for alpelisib treatment, DI and RDI will be also provided.

Dose changes: reductions, interruptions

The proportion of patients who have any dose change, i.e., any dose reduction or dose interruption will be summarized separately for each of the study treatment component and for the study treatment.

'Dose changed', 'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration eCRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively. Only dose change is collected in the eCRF, number of reductions will be derived programmatically based on the change and the direction of the change.

The following definitions are foreseen:

Reduction (alpelisib): A reduction is defined as a decrease in alpelisib dose from the protocol planned dose or a decrease from the previous non-zero dose during the dosing period, even if this decrease has been directly preceded by an interruption. A maximum of 2 dose reductions of alpelisib from the recommended starting dose may be allowed before considering discontinuation of alpelisib.

Frequency of patients reporting at least one dose reduction for alpelisib will be provided, as well as the proportion of patients with no/one/two alpelisib reductions.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Time to first alpelisib reduction (TTFAR) is defined, for subjects reporting any reduction, as time elapsed from the alpelisib start date to the date of the first reported reduction. It will be calculated as follows:

TTFAR (days)= (date of first observed alpelisib *reduction*– alpelisib *start date + 1 day)*

Time to second alpelisib reduction (TTSAR) is defined, for patients who performed two alpelisib reductions, as time elapsed from the first alpelisib reduction to the second reported reduction. It will be calculated as follows:

TTSAR (days)= (date of second observed alpelisib *reduction – date of first observed* alpelisib *reduction + 1 day)*

Summary description of time to first and time to second alpelisib reduction will be provided by means of the usual descriptive statistics.

Reduction (fulvestrant): A reduction is defined as a decrease in fulvestrant administered dose from the protocol planned dose.

Frequency of patients reporting any dose reduction for fulvestrant will be provided, and the reason under the dose reduction will be summarized.

Interruption: focusing on alpelisib, an interruption is defined as a 0 mg dose given on one or more days, after which >0 mg dose resumes. Focusing on fulvestrant, an interruption is defined as any missed injection followed by another fulvestrant administration.

Frequency of patients referring at least one interruption will be summarized separately for alpelisib and and fulvestrant, and "overall" for study treatment.

Summary of number of temporary interruptions by patient and of number of temporary interruptions by patient for subjects reporting at least one interruption will be provided considering the usual descriptive statistics. Frequency of patients reporting none/one-two/three-five/more than five temporary interruptions will also be provided.

6.4.2. Concomitant medications

Both in Core and in the Extension phase of the study, concomitant medications and significant non-drug therapies started after the start of the study treatments or before the first administration but still ongoing at the study treatments start will be summarized by ATC code (2^{nd} level) and Preferred Term.

Further information on concomitant medications taken in each study phase will be listed. For each study phase, surgical and medical procedures will be listed in the Patient Data Listings document.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Antineoplastic treatments (medications administered in both therapeutic and palliative settings) assumed by patients **after the discontinuation of the study treatment** will be summarized by ATC code (2nd level) and preferred term for each study phase.
The first antineoplastic therapy (in both therapeutic and palliative settings) administered after the discontinuation of the study treatment will also be provided according to Preferred Term and verbatim (if different from Preferred Term) considering each therapy. Drugs started on the same day will be considered as components of the same therapy (i.e., Preferred term combined in one therapy).
Radiotherapy and surgery reported after the study treatment discontinuation will be listed.

6.4.3. Adverse Events

Monitoring for adverse events take place continuously throughout the study, starting from informed consent until 30 days after the last dose of the study treatment. For details on Adverse Events definition and reporting, see *Section 8.1 - Adverse Events* of the study protocol.

For the present analysis, all events occurring (i.e., started and ended or only started) from the start of the study treatment (C1D1) of each considered study phase will be counted.

Treatment Emergent Adverse Events

An adverse event with onset date on or after the start of the first study treatment component through 30 days after the last study treatment component administration is defined as Treatment Emergent Adverse Event (TEAE). In case serious adverse events suspected to be related to study treatment occur more than 30 days after the last administration of study treatment, these were also considered as TEAEs.

Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest are defined as groups of adverse events that are of scientific and medical concern specifically for compound ribociclib or alpelisib, depending on the considered study phase.

As per study protocol the following AESIs are planned:

AESIs for ribociclib are defined as: hematologic disorders (neutropenia including febrile neutropenia, neutropenic infection and neutropenic sepsis), QT prolongation, arrhythmia, hepatic dysfunction, liver toxicity, renal failure.

AESIs for alpelisib are defined as: GI toxicity (nausea, vomiting, diarrhea), hyperglycemia, rash, hypersensitivity and anaphylactic reactions, pancreatitis, pneumonitis, severe cutaneous reactions.

A complete list of AESI by safety topic and PT to be used in AESI identification is provided by Novartis and reported in in the appendix 8.1 and 8.2 for ribociclib and alpelisib respectively. Of note, AESI safety topics provided by Novartis are updated according to the MedDRA dictionary updates and to the actual selection of AESI to be considered respect to the one

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provided by study protocol. An AESI with onset date on or after the start of the study treatment through 30 days after the last study treatment end is defined treatment emergent adverse event of special interest (TEAESI).

Separately for both study phases, an overview of TEAEs will be provided for the number of subjects with any TEAEs, any serious TEAEs, any TEAE related to study treatment and related to each component separately, any TEAEs of CTCAE grade ≥3, any TEAEs leading to discontinuation of study treatment, any TEAEs leading to dose reductions, any TEAEs leading to temporary interruption, any fatal TEAEs, any TEAEs of special interest according to the safety topic (i.e., for Ribociclib: Hepatobiliary toxicity, ILD_Pneumonitis, Infections, Myelosuppression - Anaemia, Myelosuppression - Leukopenia, Myelosuppression - Neutropenia, Myelosuppression - Other, Myelosuppression - Thrombocytopenia, Myelosuppression - Thrombocytopenia related bleeding events, QT interval prolongation, Renal toxicity, Reproductive toxicity, Second Primary Malignancies; for Alpelisib: GI toxicity Nausea Vomiting Diarrhea, Hyperglycaemia, Hypersensitivity and anaphylactic reaction, Osteonecrosis of jaw_, Pancreatitis, Pneumonitis, Rash, Severe cutaneous reactions).

The incidence of TEAEs will also be tabulated by System Organ Class (SOC) and Preferred Term (PT) using the MedDRA coding system. A subject with multiple occurrences of an AE will be counted only once in the AE category.

The incidence of TEAEs observed in at least the 10% (i.e., most common TEAE) of patients will also be summarized by SOC, PT and maximum CTCAE grade. For each subject and each adverse event, the maximum CTCAE grade will be selected. TEAEs with reasonable possibility of being related to the study treatment (each of the considered components, both components or indistinguishable) will be considered as drug-related. Drug-related TEAEs will be summarized by SOC and PT. Drug-related TEAEs with CTCAE Grade equal to or greater than 3 will be summarized by SOC and PT. Drug-related TEAEs will also be summarized separately for each component.

TEAEs leading to any study drug discontinuation regardless of study drug relationship, will be summarized by SOC and PT and CTCAE grade.

TEAEs leading to a dose modification (i.e., dose reduction or dose temporary interruption will be considered separately), regardless of study drug relationship, will be summarized by SOC and PT.

Analogous summary of serious TEAEs will also be provided. The incidence of serious TEAE will be tabulated by System Organ Class (SOC) and Preferred Term (PT) using the MedDRA coding system.

The incidence of serious TEAEs will also be summarized by SOC, PT and maximum CTCAE grade.

Serious TEAEs suspected of being study drug-related will be summarized by SOC and PT. This summary will be repeated and separately for each component. Serious TEAE suspected related of CTCAE grade ≥3 will also be summarized by SOC and PT.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

The incidence of TEAEs of special interest will be summarized by SOC and PT, and by SOC, PT and maximum CTCAE grade separately for each safety topic.

Listings of all deaths, TEAEs with a fatal outcome, non-fatal serious TEAEs, suspected related TEAEs, TEAEs with CTCAE grade ≥3, TEAEs leading to study treatment discontinuation, TEAEs leading to dose modification, TEAE of Special Interest will be provided for both study phases.

Non-treatment-emergent adverse events will be listed as well.

Liver events and Laboratory trigger definitions

Events to be considered as Liver events are detailed *in Section 14.5 - Liver event and Laboratory trigger Definitions and Follow-up Requirements* of the study protocol and are reported in the following Table 6.4.3-3.

Table 6.4.3-3 – Liver event and laboratory trigger definitions

	Definition/threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN ALP > 2 × ULN (in the absence of known bone pathology) TBL > 2 × ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 × ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms.
TBL: total bilirubin; ULN: upper limit of normal.

For each study phase, information collected in the eCRF pages "Liver Event – Overview", "Liver Event - Potential Impact of Alcohol Use (6 weeks prior to event)", "Medical History Possibly Contributing to Liver Dysfunction", "Liver Event - Drug Use 6 Months Prior to Liver Event", "Liver Event - Related Imaging", "Liver Event - Pathology", "Liver Event - Autoimmune", "Liver Event - Immunoglobulin 1", "Liver Event - Immunoglobulin 2", "Liver Event - Immunoglobulin 3", "Liver Event - Viral Serology", "Liver Event - Liver Function Tests 1", "Liver Event - Liver

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Function Tests 2", "Liver Event - Liver Function Tests 3" and "Liver Event - Acetaminophen/Paracetamol" will only be listed in Patient Data Listings document.

Alpelisib-induced skin toxicity (Extension phase only)

Skin toxicity is a class-effect adverse event observed with PI3Ki/mTORi agents. Close monitoring of potential skin reactions will be performed at each planned visit and will be reported as an adverse event. The onset is typically within the first 2 months of treatment start and is reversible with adequate comedication and treatment interruption if needed.

Information on performed assessment of skin toxicity and on collection of skin biopsy and relative result will only be listed.

6.4.4. Laboratory parameters

Laboratory parameters for hematology and chemistry assessments collected in each study phase will be summarized by means of the usual descriptive statistics over each scheduled timepoint together with their changes vs. screening. Only parameters expressed in standard unit will be considered in the summary descriptions. Of note, value of Glycated hemoglobin A1c (HbA1c), planned only in the extension phase, can be collected both according to % unit (i.e., National Glycohemoglobin Standardization Program (NGSP)) and according to mmol/mol (i.e., International Federation of Clinical Chemistry (IFCC) standardization) will be converted to % according to the following formula:

$$NGSP = [0.09148 * IFCC] + 2.152$$

(For example: HbA1c = 42 mmol/mol will be converted as % as follows: HbA1c = 0.0918*42+2.152 = 6%). Unscheduled assessments will only be listed in Patient Data Listings document.

For the Extension phase only, urinalysis parameters will be described with absolute and relative frequency of patients reporting absence/presence/Not done for each considered parameter. pH will be summarized by means of the usual descriptive statistics.

Values out of the normal ranges will be listed and only for the Extension phase the clinically significance will be also provided. For the urinalysis, only collected during the Extension phase of the study, all present parameters will be listed together with the clinically significance.

Categorization of laboratory values will be assigned programmatically as per version 4.03 of the National Cancer Institute (NCI) CTCAE. The calculation of CTCAE grades will be based purely on the observed laboratory values, clinical assessments will not be taken into account. Of note, only value collected with unit of measure and relative normal range available can be graded.

For parameter graded with CTCAE grades, the proportion of patients with altered laboratory parameters of hematology and chemistry (corresponding to CTC AE term) will also be summarized overall and by CTC grade, version 4.03, considered assessments (both scheduled

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

and unscheduled) performed before or on the start of treatment and assessments (both scheduled and unscheduled) performing after the start of treatment, separately.

Parameters to be described and relative scheduled time of collection foreseen for each study phase are summarized in tables below while further details for CTCAE grade version 4.03 are reported in the Appendix 8.3 on parameter where this grade is applicable (column 'Corresponding CTCAE Term' not equal to '-').

Core phase

Table 6.4.4-4 – Laboratory parameters and scheduled timepoint of collection for the Core phase of the study

Parameter	Standard unit	Possible corresponding CTC AE Term
Hematology (Screening, C1D15, C2D1, C2D15, C3D1, C4D1, C5D1, C6D1, D1 every 3 cycles starting with C9, EOT)		
WBC	(10^9/L)	White blood cell decreased Leukocytosis
ANC (absolute neutrophil count)	(10^9/L)	Neutrophil count decreased
Lymphocytes (absolute)	(10^9/L)	Lymphocyte count decreased Lymphocyte count increased
Lymphocytes	(%)	-
Hemoglobin	(g/L)	Anemia Hemoglobin increased
Platelets	(10^9/L)	Platelet count decreased
Chemistry (Screening, C1D15, C2D1, C2D15, C3D1, C4D1, C5D1, C6D1, D1 every 3 cycles starting with C9, EOT)		
Alkaline phosphatase	(U/L)	Alkaline phosphatase increased
ALT (SGPT)	(U/L)	Alanine aminotransferase increased
AST (SGOT)	(U/L)	Aspartate aminotransferase increased
Calcium (corrected for serum albumin)	(mmol/L)	Hypocalcemia Hypercalcemia
Creatinine	(umol/L)	Creatinine increased
Creatinine clearance	(mL/s)	-
Potassium	(mmol/L)	Hypokalemia Hyperkalemia
Sodium	(mmol/L)	Hyponatremia Hypernatremia
Magnesium	(mmol/L)	Hypomagnesemia Hypermagnesemia
Phosphorus	(mmol/L)	Hypophosphatemia
Total bilirubin	(umol/L)	Blood bilirubin increased
Direct bilirubin (if Gilbert's syndrome)	(umol/L)	-

Of note, the International normalized ratio (INR) collected at screening will be described as reported in section 6.2. Background and Demographic Characteristics.

Extension phase

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Table 6.4.4-5 – Laboratory parameters and scheduled timepoint of collection for the Extension phase of the study

Parameter	Standard unit	Possible corresponding CTC AE Term
Hematology (Screening, C1D1, C1D15, C2D1, D1 every cycle starting with C3, EOT)		
Hemoglobin	(g/L)	Anemia Hemoglobin increased
Hematocrit	(%)	-
MCH	(pg)	-
MCHC	(g/L)	-
MCV	(fL)	-
Red Blood Cells	(10^12/L)	-
WBC	(10^9/L)	White blood cell decreased Leukocytosis
Basophils	(10^9/L)	-
Eosinophils	(10^9/L)	-
Lymphocytes	(10^9/L)	Lymphocyte count decreased Lymphocyte count increased
Neutrophils	(10^9/L)	Neutrophil count decreased
Monocytes	(10^9/L)	-
Platelets	(10^9/L)	Platelet count decreased
Chemistry (Full assessment: Screening, C2D1, EOT Partial assessment: C1D1, C1D15, D1 every cycle starting with C3)		
Alkaline phosphatase	(U/L)	Alkaline phosphatase increased
ALT (SGPT) [a]	(U/L)	Alanine aminotransferase increased
AST (SGOT) [a]	(U/L)	Aspartate aminotransferase increased
Calcium (corrected for serum albumin)	(mmol/L)	Hypocalcemia Hypercalcemia
Creatinine [a]	(umol/L)	Creatinine increased
Creatinine clearance	(mL/s)	-
Potassium	(mmol/L)	Hypokalemia Hyperkalemia
Sodium	(mmol/L)	Hyponatremia Hypernatremia
Magnesium	(mmol/L)	Hypomagnesemia Hypermagnesemia
Phosphorus	(mmol/L)	Hypophosphatemia
Total bilirubin [a]	(umol/L)	Blood bilirubin increased
Direct bilirubin	(umol/L)	-
Indirect bilirubin	(umol/L)	-
C-peptide	(pmol/L)	-
Gamma-glutamyl-transferase (GGT)	(U/L)	GGT increased
Total protein	(g/L)	-
Albumin	(g/L)	Hypoalbuminemia
Creatin-Kinase (CK) [a]	(U/L)	CPK increased

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Blood Urea Nitrogen (BUN)	(mmol/L)	-
Urea	(mmol/L)	-
Uric Acid	(umol/L)	Hyperuricemia
Lactate dehydrogenase (LDH)	(U/L)	-
Glucose metabolism (Plasma Glucose fasting or random: Screening (only fasting), C1D1, C1D8, C1D15, C2D1, C2D15, D1 every cycle starting with C3, EOT; HbA1C: Screening, C2D1 and then every 3 cycles (i.e., C5D1, C8D1 …)		
Plasma glucose (fasting)	(mmol/L)	Hypoglycemia Hyperglycemia
Plasma glucose (random) [b]	(mmol/L)	Hypoglycemia Hyperglycemia
HbA1C	(%)	-
Fasting lipid panel (assessments: Screening, EOT)		
Total cholesterol (fasting)	(mmol/L)	Cholesterol high
LDL (fasting)	(mmol/L)	-
HDL (fasting)	(mmol/L)	-
Triglycerides (fasting)	(mmol/L)	Hypertriglyceridemia
Pancreatic enzymes: (assessments: Screening, C3D1, EOT + when clinically indicated)		
Amylase (fasting)	(U/L)	Serum amylase increased
Lipase (fasting)	(U/L)	Lipase increased
Urinalysis (Screening, EOT + when clinically indicated)		
pH	-	-
WBC	-	-
Blood	-	-
Protein	-	-
Glucose	-	-

[a] Partial assessment at C1D1, C1D15, D1 every cycle starting with C3.

[b] This parameter will be only listed and considered for possible corresponding CTC AE Term.

Of note, the International normalized ratio (INR), activated partial thromboplastin time (aPTT) and partial thromboplastin time (PTT) collected at screening will be described as reported in section 6.2. Background and Demographic Characteristics.

6.4.5. Vital signs/Physical examination

Vital signs

In each study phase, the collected vital signs (i.e., weight, body mass index, body temperature, pulse, systolic and diastolic blood pressures) will be summarized by scheduled timepoint by means of the usual descriptive statistics. Changes vs. screening values will also be considered.

6.4.6. Other safety parameters

ECG (standard 12 lead)

In each study phase, standard 12 lead ECG assessments are performed locally at screening, C1D15, C2D1, thereafter as clinically indicated and at EOT visit. QT interval corrected by Fridericia's formula (QTcF) is recorded and used for trial eligibility and safety assessments.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

The summary description of patients performing ECG at each scheduled timepoint and the frequency of subjects reporting any new clinically significant abnormality will be provided.

The QT corrected interval using Fridericia formula will be described at each planned evaluation performed by patients (i.e., screening, C1D15, C2D1, EoT for patients who discontinued the study due to disease progression) together with its change vs. screening. Unscheduled visit will be listed. Collected summaries of resting heart rate, PR duration, QT duration and QRS duration at each scheduled and unscheduled timepoint will also be listed.

The proportion of patients reporting a QTCF value greater than or equal to 480 msec at least once during the considered study phase will be calculated considering also the unplanned performed ECGs. The frequency of patients reporting a QTCF value greater than or equal to 501 msec at least once will also be summarized.

Cardiac imaging

In Extension phase only, a cardiac imaging is planned at screening and EOT (for patients who discontinued the study for progressive disease only).

Frequency of patients performing cardiac imaging at each scheduled timepoint will be provided, as well as the patient's distribution considering the imaging method. Descriptive statistics of Left Ventricular Ejection Fraction will be provided, as well as a summary description of the overall interpretation.

ECOG performance status

In each study phase, ECOG performance status categories will be described at each scheduled timepoint by means of absolute and relative frequencies.

6.5. Subgroup Analyses

Not applicable for the present analysis. All the subgroups defined in the efficacy analysis are described in the corresponding above sections.

6.6. Interim Analysis and Data Monitoring

Several interim analyses and post-hoc analyses were conducted on BioItaLEE Core phase data. The content of each conducted analysis is summarized in the following Table 6.6-1.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Table 6.6-1 – Interim analyses and post-hoc analyses performed on Core phase data

Analysis	Date of Data Base Freeze	Cut-off date	Median Follow-up	Considered Data	Content of analysis
First IA	27Mar2019	-	-	All baseline data of patients valid for BAS	Patients' baseline data on demography, disease condition and liquid biopsy results. NGS analysis results obtained with BioItaLEE Custom panel (39 genes analyzed to identify occurred hotspot mutations) and Oncomine™ Pan-Cancer Cell-Free Assay (Thermofisher) panel (12 genes analyzed to identify the occurred CNV amplifications) were described, as well as results on alterations detected on considered gene clusters.
Second IA	23May2019	-	-	All baseline data of patients valid for BAS + First imaging evaluation data	NGS analysis baseline result (hotspot mutations on 39 genes belonging to BioItaLEE Custom panel and CNV amplifications on 12 genes belonging to Pan-Cancer panel + gene clusters) on liquid biopsy + Tumor response at first imaging evaluation, early overall response rate and early clinical benefit rate.
Third IA	20Dec2019	For each patient, the 224th days after their C1D1 visit	225 days of exposure to study treatment	All data collected up to the cut-off date for each patient	NGS analysis baseline result (hotspot mutations identified for genes belonging to BioItaLEE and Pan-Cancer panel + gene clusters) on liquid biopsy and on tissue (recent and archival) and their agreement+ Tumor response, best overall response, overall response rate, clinical benefit rate, early progression rate, PFS, TTP, Tumor shrinkage for patients with measurable disease + AE, study drug exposure, ECG results.
Fourth IA	08May2020	15Oct2019	366 days of exposure to study treatment	All data collected up to the cut-off date for each patient	NGS analysis baseline result (hotspot mutations identified for genes belonging to BioItaLEE panel + gene clusters + Target mutation) on liquid biopsy + clinical responses (tumor response, BOR, CBR, PFS, TTP, TTR, tumor shrinkage) + TK1 serum levels + association of Target mutation over time and of TK1 levels over time with clinical responses + AE, study drug exposure, ECG results.

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Post-hoc of 4th IA	-	15Oct2019	-	TK1 serum levels	Additional analysis on TK1, identification of best categorization to apply to TK1 values. + TK1 class and clinical response + additional analysis on target mutation + comparison of PIK3CA mutations observed in liquid biopsy and tissue at screening
Fifth IA	16Mar2021	15Oct2020	26.9 months	All data collected up to the cut-off date for each patient	NGS analysis baseline result (hotspot mutations identified for genes belonging to BioItaLEE panel + gene clusters + Target mutation [redacted]) on liquid biopsy + clinical responses (tumor response, BOR, CBR, early progression rate, PFS, TTP, TTR, tumor shrinkage) + TK1 serum levels + association of dynamic ctDNA over time and of dynamic TK1 change over time with clinical responses + AE, AESI, study drug exposure, ECG results, subsequent antineoplastic therapy.
First post-hoc of 5th IA	-	15Oct2020	-	Additional analysis on NGS results and TK1 serum levels	Association of NGS results (mutational status at screening, mutation presence/absence at C1D15) and clinical outcome (PFS) + Association of TK1 levels (different classifications applied) and clinical outcome (PFS)
Second post-hoc of 5th IA	-	15Oct2020	-	Additional analysis on NGS results and TK1 serum levels	Association of NGS results and TK1 levels over time with clinical outcome (PFS)
[redacted]					
Fourth post-hoc of 5th IA	-	15Oct2020	-	Additional analysis on NGS results and TK1 serum levels	Biomarker and clinical response (ORR, CBR) association. New categories of biomarkes dynamic change are considered both singularly (early dynamic change of ctDNA at C1D15 and dynamic change of TK1) and combined (classes considering both TK1 and target mutation VAF at C1D15)

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

[redacted]

Statistical Analysis Plan

Sponsor: Novartis

Protocol number: CLEE011AIT01

[redacted]

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7. REFERENCES

[1] Therasse, et al 2000, New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16

[2] Eisenhauer, et al 2009, European Journal of Cancer; 45:228-247.

8. APPENDIX

8.1. Preferred Term to identify Adverse Event of Special Interest (AESI) for Ribociclib

Safety Topic	Preferred Term
Hepatobiliary toxicity	5'nucleotidase increased, AST to platelet ratio index increased, AST/ALT ratio abnormal, Acquired antithrombin III deficiency, Acquired factor IX deficiency, Acquired factor V deficiency, Acquired factor VIII deficiency, Acquired factor XI deficiency, Acquired hepatocerebral degeneration, Acquired protein S deficiency, Acute graft versus host disease in liver, Acute hepatic failure, Acute on chronic liver failure, Acute yellow liver atrophy, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Allergic hepatitis, Alloimmune hepatitis, Ammonia abnormal, Ammonia increased, Anorectal varices, Anorectal varices haemorrhage, Anti factor X activity abnormal, Anti factor X activity decreased, Anti factor X activity increased, Anti-liver cytosol antibody type 1 positive, Antithrombin III decreased, Ascites, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Asterixis, Autoimmune hepatitis, Bacterascites, Benign hepatic neoplasm, Benign hepatobiliary neoplasm, Bile acids abnormal, Bile acids increased, Bile output abnormal, Bile output decreased, Biliary ascites, Biliary cirrhosis, Biliary fibrosis, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Bilirubin excretion disorder, Bilirubin urine present, Biopsy liver abnormal, Blood alkaline phosphatase abnormal, Blood alkaline phosphatase increased, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Blood cholinesterase abnormal, Blood cholinesterase decreased, Blood fibrinogen abnormal, Blood fibrinogen decreased, Blood thrombin abnormal, Blood thrombin decreased, Blood thromboplastin abnormal, Blood thromboplastin decreased, Bromosulphthalein test abnormal, Cardiohepatic syndrome, Child-Pugh-Turcotte score abnormal, Child-Pugh-Turcotte score increased, Cholaemia, Cholangiosarcoma, Cholestasis, Cholestatic liver injury, Cholestatic pruritus, Chronic graft versus host disease in liver, Chronic hepatic failure, Chronic hepatitis, Coagulation factor IX level abnormal, Coagulation factor IX level decreased, Coagulation factor V level abnormal, Coagulation factor V level decreased, Coagulation factor VII level abnormal, Coagulation factor VII level decreased, Coagulation factor X level abnormal, Coagulation factor X level decreased, Coagulation factor decreased, Coma hepatic, Complications of transplanted liver, Computerised tomogram liver abnormal, Congestive hepatopathy, Cryptogenic cirrhosis, Cytokeratin 18 increased, Deficiency of bile secretion, Diabetic hepatopathy, Drug-induced liver injury, Duodenal varices, Flood syndrome, Focal nodular hyperplasia, Foetor hepaticus, Galactose elimination capacity test abnormal, Galactose elimination capacity test decreased, Gallbladder varices, Gamma-glutamyltransferase abnormal, Gamma-glutamyltransferase increased, Gastric variceal injection, Gastric variceal ligation, Gastric varices, Gastric varices haemorrhage, Gastrooesophageal variceal haemorrhage prophylaxis, Glutamate dehydrogenase increased, Glycocholic acid increased, Graft versus host disease in liver, Granulomatous liver disease, Guanase increased, Haemangioma of liver, Haemorrhagic ascites, Haemorrhagic hepatic cyst, Hepaplastin abnormal, Hepaplastin decreased, Hepatectomy, Hepatic adenoma, Hepatic angiosarcoma, Hepatic artery flow decreased, Hepatic atrophy, Hepatic calcification, Hepatic cancer, Hepatic cancer metastatic, Hepatic cancer recurrent, Hepatic cancer stage I, Hepatic cancer stage II, Hepatic cancer stage III, Hepatic cancer stage IV, Hepatic cirrhosis, Hepatic cyst, Hepatic cyst ruptured, Hepatic cytolysis, Hepatic encephalopathy, Hepatic encephalopathy prophylaxis, Hepatic enzyme abnormal, Hepatic enzyme decreased, Hepatic enzyme increased, Hepatic failure, Hepatic fibrosis, Hepatic fibrosis marker abnormal, Hepatic fibrosis marker

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Safety Topic	Preferred Term
	increased, Hepatic function abnormal, Hepatic haemangioma rupture, Hepatic hamartoma, Hepatic hydrothorax, Hepatic hypertrophy, Hepatic hypoperfusion, Hepatic infiltration eosinophilic, Hepatic lesion, Hepatic lipoma, Hepatic lymphocytic infiltration, Hepatic mass, Hepatic necrosis, Hepatic neoplasm, Hepatic neuroendocrine tumour, Hepatic pain, Hepatic perfusion disorder, Hepatic sarcoma, Hepatic sequestration, Hepatic steato-fibrosis, Hepatic steatosis, Hepatic vascular resistance increased, Hepatic venous pressure gradient abnormal, Hepatic venous pressure gradient increased, Hepatitis, Hepatitis A immunity confirmed, Hepatitis B immunity confirmed, Hepatitis E immunity confirmed, Hepatitis acute, Hepatitis cholestatic, Hepatitis chronic active, Hepatitis chronic persistent, Hepatitis fulminant, Hepatitis toxic, Hepatobiliary cancer, Hepatobiliary cancer in situ, Hepatobiliary cyst, Hepatobiliary disease, Hepatobiliary neoplasm, Hepatobiliary scan abnormal, Hepatoblastoma, Hepatoblastoma recurrent, Hepatocellular carcinoma, Hepatocellular foamy cell syndrome, Hepatocellular injury, Hepatomegaly, Hepatopulmonary syndrome, Hepatorenal failure, Hepatorenal syndrome, Hepatosplenomegaly, Hepatotoxicity, Hyperammonaemia, Hyperbilirubinaemia, Hypercholia, Hyperfibrinolysis, Hypertransaminasaemia, Hypoalbuminaemia, Hypocoagulable state, Hypofibrinogenaemia, Hypoprothrombinaemia, Hypothrombinaemia, Hypothromboplastinaemia, Icterus index increased, Immune-mediated cholangitis, Immune-mediated hepatic disorder, Immune-mediated hepatitis, Increased liver stiffness, International normalised ratio abnormal, International normalised ratio increased, Intestinal varices, Intestinal varices haemorrhage, Intrahepatic portal hepatic venous fistula, Ischaemic hepatitis, Jaundice, Jaundice cholestatic, Jaundice hepatocellular, Kayser-Fleischer ring, Leucine aminopeptidase increased, Liver and pancreas transplant rejection, Liver carcinoma ruptured, Liver dialysis, Liver disorder, Liver function test abnormal, Liver function test decreased, Liver function test increased, Liver induration, Liver injury, Liver iron concentration abnormal, Liver iron concentration increased, Liver opacity, Liver operation, Liver palpable, Liver sarcoidosis, Liver scan abnormal, Liver tenderness, Liver transplant, Liver transplant failure, Liver transplant rejection, Liver-kidney microsomal antibody positive, Lupoid hepatic cirrhosis, Lupus hepatitis, Magnetic resonance imaging hepatobiliary abnormal, Magnetic resonance proton density fat fraction measurement, Mitochondrial aspartate aminotransferase increased, Mixed hepatocellular cholangiocarcinoma, Mixed liver injury, Model for end stage liver disease score abnormal, Model for end stage liver disease score increased, Molar ratio of total branched-chain amino acid to tyrosine, Multivisceral transplantation, Nodular regenerative hyperplasia, Non-alcoholic fatty liver, Non-alcoholic steatohepatitis, Non-cirrhotic portal hypertension, Ocular icterus, Oedema due to hepatic disease, Oesophageal varices haemorrhage, Omental oedema, Osteopontin increased, Parenteral nutrition associated liver disease, Perihepatic discomfort, Peripancreatic varices, Periportal oedema, Peritoneal fluid protein abnormal, Peritoneal fluid protein decreased, Peritoneal fluid protein increased, Peritoneovenous shunt, Pneumobilia, Portal fibrosis, Portal hypertension, Portal hypertensive biliopathy, Portal hypertensive colopathy, Portal hypertensive enteropathy, Portal hypertensive gastropathy, Portal shunt, Portal shunt procedure, Portal tract inflammation, Portal vein cavernous transformation, Portal vein dilatation, Portal vein flow decreased, Portal vein pressure increased, Portopulmonary hypertension, Primary biliary cholangitis, Protein C decreased, Protein S abnormal, Protein S decreased, Prothrombin level abnormal, Prothrombin level decreased, Prothrombin time abnormal, Prothrombin time prolonged, Prothrombin time ratio abnormal, Prothrombin time ratio increased, Radiation hepatitis, Regenerative siderotic hepatic nodule, Renal and liver transplant, Retinol binding protein decreased, Retrograde portal vein flow, Reye's syndrome, Reynold's syndrome, Small-for-size liver syndrome, Spider naevus, Splenic artery embolisation, Splenic varices, Splenic varices haemorrhage, Splenorenal shunt, Splenorenal shunt procedure, Spontaneous bacterial peritonitis, Spontaneous intrahepatic portosystemic venous shunt, Steatohepatitis, Stomal varices, Subacute hepatic failure, Sugiura procedure, Suspected drug-induced liver injury, Thrombin time abnormal, Thrombin time prolonged, Transaminases abnormal, Transaminases increased, Transient hepatic attenuation differences, Ultrasound liver abnormal, Urine bilirubin increased, Urobilinogen urine decreased, Urobilinogen urine increased, Varices oesophageal, Varicose veins of abdominal wall, White nipple sign, X-ray hepatobiliary abnormal, Yellow skin
ILD_Pneumonitis	Acute interstitial pneumonitis, Acute lung injury, Acute respiratory distress syndrome, Airway remodelling, Allergic eosinophilia, Alveolar lung disease, Alveolar proteinosis, Alveolitis, Alveolitis necrotising, Antisynthetase syndrome, Autoimmune lung disease, Biopsy lung abnormal, Bronchiolitis, Bronchiolitis obliterans syndrome, Chronic graft versus host disease in lung, Combined pulmonary

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Safety Topic	Preferred Term
	fibrosis and emphysema, Complications of transplanted lung, Confirmed e-cigarette or vaping product use associated lung injury, Cystic lung disease, Diffuse alveolar damage, Eosinophilia myalgia syndrome, Eosinophilic granulomatosis with polyangiitis, Eosinophilic pneumonia, Eosinophilic pneumonia acute, Eosinophilic pneumonia chronic, Goodpasture's syndrome, Granulomatosis with polyangiitis, Granulomatous pneumonitis, Hypersensitivity pneumonitis, Idiopathic interstitial pneumonia, Idiopathic pneumonia syndrome, Idiopathic pulmonary fibrosis, Immune-mediated lung disease, Interstitial lung abnormality, Interstitial lung disease, Langerhans' cell histiocytosis, Low lung compliance, Lung induration, Lung infiltration, Lung opacity, Lung transplant rejection, Lupus pneumonitis, Lymphangioleiomyomatosis, Necrotising bronchiolitis, Obliterative bronchiolitis, Organising pneumonia, Pleuroparenchymal fibroelastosis, Pneumonitis, Pneumonitis chemical, Polyarteritis nodosa, Probable e-cigarette or vaping product use associated lung injury, Progressive massive fibrosis, Pulmonary alveolar haemorrhage, Pulmonary bullae rupture, Pulmonary eosinophilia, Pulmonary fibrosis, Pulmonary granuloma, Pulmonary haemosiderosis, Pulmonary necrosis, Pulmonary radiation injury, Pulmonary renal syndrome, Pulmonary sarcoidosis, Pulmonary septal thickening, Pulmonary toxicity, Pulmonary vasculitis, Radiation alveolitis, Radiation bronchitis, Radiation fibrosis - lung, Radiation pneumonitis, Restrictive pulmonary disease, Rheumatoid arthritis-associated interstitial lung disease, Rheumatoid lung, Sarcoidosis, Small airways disease, Systemic sclerosis pulmonary, Toxic oil syndrome, Transfusion-related acute lung injury
Infections	Encephalomyelitis bacterial, Encephalomyelitis rubella, Encephalomyelitis viral, End stage AIDS, Endemic syphilis, Endocarditis, Endocarditis Q fever, Endocarditis bacterial, Endocarditis candida, Endocarditis enterococcal, Endocarditis gonococcal, Endocarditis haemophilus, Endocarditis helminthic, Endocarditis histoplasma, Endocarditis meningococcal, Endocarditis pseudomonal, Endocarditis rheumatic, Endocarditis staphylococcal, Endocarditis syphilitic, Endocarditis viral, Endometritis, Endometritis bacterial, Endometritis gonococcal, Endophthalmitis, Endotoxaemia, Endotoxic shock, Enteritis infectious, Enteritis necroticans, Enterobacter bacteraemia, Enterobacter infection, Enterobacter pneumonia, Enterobacter sepsis, Enterobacter tracheobronchitis, Enterobiasis, Enterococcal bacteraemia, Enterococcal gastroenteritis, Enterococcal infection, Enterococcal sepsis, Enterocolitis AIDS, Enterocolitis bacterial, Enterocolitis fungal, Enterocolitis helminthic, Enterocolitis infectious, Enterocolitis viral, Enterovirus infection, Enterovirus myocarditis, Ependymitis, Epidemic pleurodynia, Epidemic polyarthritis, Epidemic typhus, Epidermodysplasia verruciformis, Epididymitis, Epididymitis blastomyces, Epididymitis mumps, Epididymitis tuberculous, Epididymitis ureaplasmal, Epididymo-orchitis gonococcal, Epiglottic abscess, Epiglottitis, Epiglottitis haemophilus, Epiglottitis obstructive, Epstein Barr virus positive mucocutaneous ulcer, Epstein-Barr viraemia, Epstein-Barr virus associated lymphoma, Epstein-Barr virus associated lymphoproliferative disorder, Epstein-Barr virus infection, Epstein-Barr virus infection reactivation, Eruptive pseudoangiomatosis, Erysipelas, Erysipeloid, Erysipelothrix infection, Erysipelothrix sepsis, Erythema induratum, Erythema infectiosum, Erythema marginatum, Erythema migrans, Erythrasma, Escherichia bacteraemia, Escherichia infection, Escherichia peritonitis, Escherichia pyelonephritis, Escherichia sepsis, Escherichia urinary tract infection, Escherichia vaginitis, Eubacterium infection, Exanthema subitum, Exserohilum infection, External ear cellulitis, Extradural abscess, Extrapulmonary tuberculosis, Eye abscess, Eye infection, Eye infection bacterial, Eye infection chlamydial, Eye infection fungal, Eye infection gonococcal, Eye infection helminthic, Eye infection intraocular, Eye infection staphylococcal, Eye infection syphilitic, Eye infection toxoplasmal, Eye infection viral, Eyelid boil, Eyelid folliculitis, Eyelid infection, Faecal-oral transmission of infection, Fallopian tube abscess, Fascial infection, Fascioliasis, Fasciolopsiasis, Fatal familial insomnia, Febrile infection, Febrile infection-related epilepsy syndrome, Female genital tract tuberculosis, Femoral hernia gangrenous, Filariasis, Filariasis lymphatic, Filovirus infection, Flavivirus infection, Flavobacterium infection, Flea infestation, Focal epithelial hyperplasia, Focal peritonitis, Follicular cystitis, Folliculitis, Folliculitis barbae, Folliculitis genital, Food poisoning, Foot and mouth disease, Fournier's gangrene, Fracture infection, Fungaemia, Fungal abscess central nervous system, Fungal balanitis, Fungal cystitis, Fungal disease carrier, Fungal endocarditis, Fungal foot infection, Fungal infection, Fungal labyrinthitis, Fungal myositis, Fungal oesophagitis, Fungal paronychia, Fungal peritonitis, Fungal pharyngitis, Fungal retinitis, Fungal rhinitis, Fungal sepsis, Fungal skin infection, Fungal tracheitis, Fungal urethritis, Funguria, Funisitis, Furuncle, Fusarium endocarditis, Fusarium infection, Fusobacterium infection, Gallbladder abscess, Gallbladder empyema, Gangrene, Gangrene neonatal, Gangrenous balanitis, Gardnerella infection, Gas gangrene, Gastric infection, Gastric ulcer

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Safety Topic	Preferred Term
	helicobacter, Gastritis bacterial, Gastritis fungal, Gastritis helminthic, Gastritis herpes, Gastritis viral, Gastroenteritis, Gastroenteritis Escherichia coli, Gastroenteritis adenovirus, Gastroenteritis aerobacter, Gastroenteritis aeromonas, Gastroenteritis astroviral, Gastroenteritis bacillus, Gastroenteritis bacterial, Gastroenteritis caliciviral, Gastroenteritis clostridial, Gastroenteritis cryptococcal, Gastroenteritis cryptosporidial, Gastroenteritis enteroviral, Gastroenteritis listeria, Gastroenteritis norovirus, Gastroenteritis paracolon bacillus, Gastroenteritis proteus, Gastroenteritis pseudomonas, Gastroenteritis rotavirus, Gastroenteritis salmonella, Gastroenteritis sapovirus, Gastroenteritis shigella, Gastroenteritis staphylococcal, Gastroenteritis vibrio, Gastroenteritis viral, Gastroenteritis yersinia, Gastrointestinal anthrax, Gastrointestinal bacterial infection, Gastrointestinal bacterial overgrowth, Gastrointestinal candidiasis, Gastrointestinal fungal infection, Gastrointestinal gangrene, Gastrointestinal infection, Gastrointestinal mucormycosis, Gastrointestinal protozoal infection, Gastrointestinal viral infection, Generalised vaccinia, Genital abscess, Genital candidiasis, Genital herpes, Genital herpes simplex, Genital herpes zoster, Genital infection, Genital infection bacterial, Genital infection female, Genital infection fungal, Genital infection helminthic, Genital infection male, Genital infection viral, Genital ulcer syndrome, Genitourinary chlamydia infection, Genitourinary tract gonococcal infection, Genitourinary tract infection, Geotrichum infection, Gerstmann Straussler Scheinker syndrome, Gianotti-Crosti syndrome, Giant fornix syndrome, Giardiasis, Gingival abscess, Gingivitis, Gnathostomiasis, Gonococcal heart disease, Gonococcal infection, Gonococcal pelvic inflammatory disease, Gonorrhoea, Gradenigo's syndrome, Graft infection, Granulicatella bacteraemia, Granulicatella infection, Granuloma inguinale, Granulomatous lymphadenitis, Green nail syndrome, Groin abscess, Groin infection, Group B streptococcus neonatal sepsis, Guillain-Barre syndrome, Gynaecological chlamydia infection, H1N1 influenza, H2N2 influenza, H3N2 influenza, HCoV-229E infection, HCoV-HKU1 infection, HCoV-NL63 infection, HCoV-OC43 infection, HIV associated nephropathy, HIV cardiomyopathy, HIV carrier, HIV enteropathy, HIV infection, HIV infection CDC Group I, HIV infection CDC Group II, HIV infection CDC Group III, HIV infection CDC Group IV subgroup A, HIV infection CDC Group IV subgroup B, HIV infection CDC Group IV subgroup C1, HIV infection CDC Group IV subgroup C2, HIV infection CDC Group IV subgroup D, HIV infection CDC Group IV subgroup E, HIV infection CDC category A, HIV infection CDC category B, HIV infection CDC category C, HIV infection CDC group IV, HIV infection WHO clinical stage I, HIV infection WHO clinical stage II, HIV infection WHO clinical stage III, HIV infection WHO clinical stage IV, HIV lipodystrophy, HIV meningoencephalitis, HIV peripheral neuropathy, HIV viraemia, HIV wasting syndrome, HIV-2 infection, HIV-associated neurocognitive disorder, HTLV-1 carrier, Haematological infection, Haematoma infection, Haemophilus bacteraemia, Haemophilus infection, Haemophilus sepsis, Haemorrhagic fever, Haemorrhagic fever with renal syndrome, Haemorrhagic pneumonia, Haemorrhagic varicella syndrome, Haemorrhoid infection, Hand-foot-and-mouth disease, Hantaviral infection, Hantavirus pulmonary infection, Heartland virus infection, Helicobacter duodenal ulcer, Helicobacter duodenitis, Helicobacter gastritis, Helicobacter infection, Helicobacter sepsis, Helminthic infection, Hepatic actinomycosis, Hepatic amoebiasis, Hepatic candidiasis, Hepatic cyst infection, Hepatic echinococciasis, Hepatic gas gangrene, Hepatic infection, Hepatic infection bacterial, Hepatic infection fungal, Hepatic infection helminthic, Hepatitis A, Hepatitis B, Hepatitis B reactivation, Hepatitis C, Hepatitis D, Hepatitis E, Hepatitis F, Hepatitis G, Hepatitis H, Hepatitis chronic active, Hepatitis chronic persistent, Hepatitis fulminant, Hepatitis infectious mononucleosis, Hepatitis mumps, Hepatitis non-A non-B, Hepatitis non-A non-B non-C, Hepatitis post transfusion, Hepatitis syphilitic, Hepatitis toxoplasmal, Hepatitis viral, Hepatitis virus-associated nephropathy, Hepatobiliary infection, Hepatosplenic abscess, Hepatosplenic candidiasis, Hernia gangrenous, Herpangina, Herpes dermatitis, Herpes oesophagitis, Herpes ophthalmic, Herpes pharyngitis, Herpes sepsis, Herpes simplex, Herpes simplex bronchitis, Herpes simplex cervicitis, Herpes simplex colitis, Herpes simplex encephalitis, Herpes simplex gastritis, Herpes simplex hepatitis, Herpes simplex meningitis, Herpes simplex meningoencephalitis, Herpes simplex meningomyelitis, Herpes simplex necrotising retinopathy, Herpes simplex oesophagitis, Herpes simplex otitis externa, Herpes simplex pharyngitis, Herpes simplex pneumonia, Herpes simplex reactivation, Herpes simplex sepsis, Herpes simplex viraemia, Herpes simplex virus conjunctivitis neonatal, Herpes simplex virus urethritis, Herpes simplex visceral, Herpes virus infection, Herpes zoster, Herpes zoster cutaneous disseminated, Herpes zoster disseminated, Herpes zoster infection neurological, Herpes zoster meningitis, Herpes zoster meningoencephalitis, Herpes zoster meningomyelitis, Herpes zoster meningoradiculitis, Herpes zoster necrotising retinopathy, Herpes zoster oticus, Herpes zoster

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Safety Topic	Preferred Term
	pharyngitis, Herpes zoster reactivation, Herpetic radiculopathy, Heterophyiasis, Hiatal hernia gangrenous, Hirudiniasis, Histoplasmosis, Histoplasmosis cutaneous, Histoplasmosis disseminated, Hookworm infection, Hordeolum, Human T-cell lymphocytic virus type II infection, Human T-cell lymphotropic virus infection, Human T-cell lymphotropic virus type I infection, Human anaplasmosis, Human bocavirus infection, Human ehrlichiosis, Human herpesvirus 6 encephalitis, Human herpesvirus 6 infection, Human herpesvirus 6 infection reactivation, Human herpesvirus 7 infection, Human herpesvirus 8 infection, Human immunodeficiency virus transmission, Human polyomavirus infection, Hydrocele male infected, Hymenolepiasis, Hyperparasitaemia, Hypopyon, Iatrogenic infection, Ileal gangrene, Immune reconstitution inflammatory syndrome associated Kaposi's sarcoma, Immune reconstitution inflammatory syndrome associated tuberculosis, Impetigo, Implant site abscess, Implant site cellulitis, Implant site infection, Implant site pustules, Incision site abscess, Incision site cellulitis, Incisional hernia gangrenous, Inclusion conjunctivitis, Inclusion conjunctivitis neonatal, Indeterminate leprosy, Indirect infection transmission, Induced abortion infection, Infantile acropustulosis, Infantile septic granulomatosis, Infected aural fistula, Infected bite, Infected bunion, Infected cyst, Infected dermal cyst, Infected fistula, Infected gouty tophus, Infected large intestinal ulcer, Infected lymphocele, Infected metastasis, Infected naevus, Infected neoplasm, Infected seroma, Infected skin ulcer, Infected urinoma, Infected varicose vein, Infected vasculitis, Infection, Infection in an immunocompromised host, Infection masked, Infection parasitic, Infection protozoal, Infection reactivation, Infection susceptibility increased, Infection transmission via personal contact, Infection via vaccinee, Infectious crystalline keratopathy, Infectious disease carrier, Infectious iridocyclitis, Infectious mononucleosis, Infectious pleural effusion, Infectious thyroiditis, Infective aneurysm, Infective aortitis, Infective chondritis, Infective corneal ulcer, Infective episcleritis, Infective exacerbation of asthma, Infective exacerbation of bronchiectasis, Infective exacerbation of chronic obstructive airways disease, Infective glossitis, Infective iritis, Infective keratitis, Infective mesenteric panniculitis, Infective myositis, Infective pericardial effusion, Infective periostitis, Infective pulmonary exacerbation of cystic fibrosis, Infective scleritis, Infective spondylitis, Infective tenosynovitis, Infective thrombosis, Infective uveitis, Infestation, Influenza, Influenza myocarditis, Infusion site abscess, Infusion site cellulitis, Infusion site infection, Infusion site joint infection, Infusion site pustule, Inguinal hernia gangrenous, Injection site abscess, Injection site cellulitis, Injection site infection, Injection site joint infection, Injection site pustule, Instillation site abscess, Instillation site infection, Instillation site pustules, Intervertebral discitis, Intestinal fistula infection, Intestinal gangrene, Intestinal schistosomiasis, Intestinal sepsis, Intestinal tuberculosis, Intracranial infection, Intrauterine gas, Intrauterine infection, Isosporiasis, JC virus granule cell neuronopathy, JC virus infection, Jamestown Canyon encephalitis, Jamestown Canyon virus infection, Janeway lesion, Japanese spotted fever, Jejunal gangrene, Joint abscess, Joint tuberculosis, Kaposi sarcoma inflammatory cytokine syndrome, Kaposi's sarcoma, Kaposi's sarcoma AIDS related, Kawasaki's disease, Keratitis bacterial, Keratitis fungal, Keratitis viral, Keratoconjunctivitis measles, Keratoderma blenorrhagica, Keratosis gonococcal, Keratouveitis, Kerion, Kidney infection, Klebsiella bacteraemia, Klebsiella infection, Klebsiella pneumoniae invasive syndrome, Klebsiella sepsis, Klebsiella urinary tract infection, Kuru, Kyasanur Forest disease, Labyrinthitis, Lacrimal gland abscess, Lacrimal sac cellulitis, Lactobacillus bacteraemia, Lactobacillus infection, Large intestine infection, Laryngeal cryptococcosis, Laryngeal papilloma, Laryngitis, Laryngitis bacterial, Laryngitis fungal, Laryngitis viral, Laryngopharyngitis, Laryngotracheitis obstructive, Lassa fever, Latent syphilis, Latent tuberculosis, Leclercia bacteraemia, Legionella infection, Leishmaniasis, Lemierre syndrome, Lentivirus infection, Lepromatous leprosy, Leprosy, Leptospira sepsis, Leptospirosis, Leptotrichia infection, Leuconostoc infection, Lice infestation, Lineal gingival erythema, Lip infection, Listeraemia, Listeria encephalitis, Listeria sepsis, Listeriosis, Liver abscess, Lobomycosis, Localised infection, Lochial infection, Louping ill, Lower respiratory tract herpes infection, Lower respiratory tract infection, Lower respiratory tract infection bacterial, Lower respiratory tract infection fungal, Lower respiratory tract infection viral, Ludwig angina, Lujo haemorrhagic fever, Lung abscess, Lupus vulgaris, Lyme arthritis, Lyme carditis, Lyme disease, Lymph gland infection, Lymph node abscess, Lymph node tuberculosis, Lymphadenitis bacterial, Lymphadenitis fungal, Lymphadenitis helminthic, Lymphadenitis viral, Lymphangitis, Lymphogranuloma venereum, Lymphoma AIDS related, Malacoplakia, Malacoplakia gastrointestinal, Malacoplakia of bone, Malacoplakia vesicae, Malaria, Malaria recrudescence, Malaria relapse, Malarial myocarditis, Malassezia infection, Male genital tract tuberculosis, Malignant syphilis, Mammary tuberculosis, Mansonellosis, Marburg disease, Mastitis, Mastitis bacterial, Mastitis fungal,

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Safety Topic	Preferred Term
	Mastitis postpartum, Mastoid abscess, Mastoid empyema, Mastoiditis, Mastoiditis fungal, Measles, Measles meningitis, Measles post vaccine, Mediastinal abscess, Mediastinitis, Medical device site abscess, Medical device site cellulitis, Medical device site infection, Medical device site joint infection, Medical device site pustule, Meningitis, Meningitis Escherichia, Meningitis aseptic, Meningitis aspergillus, Meningitis bacterial, Meningitis borrelia, Meningitis candida, Meningitis coccidioides, Meningitis coxsackie viral, Meningitis cronobacter, Meningitis cryptococcal, Meningitis echo viral, Meningitis enterococcal, Meningitis enteroviral, Meningitis exserohilum, Meningitis fungal, Meningitis gonococcal, Meningitis haemophilus, Meningitis herpes, Meningitis histoplasma, Meningitis leptospiral, Meningitis listeria, Meningitis meningococcal, Meningitis mumps, Meningitis neonatal, Meningitis pneumococcal, Meningitis salmonella, Meningitis staphylococcal, Meningitis streptococcal, Meningitis toxoplasmal, Meningitis trypanosomal, Meningitis tuberculous, Meningitis viral, Meningococcal bacteraemia, Meningococcal carditis, Meningococcal infection, Meningococcal sepsis, Meningoencephalitis amoebic, Meningoencephalitis bacterial, Meningoencephalitis helminthic, Meningoencephalitis herpes simplex neonatal, Meningoencephalitis herpetic, Meningoencephalitis viral, Meningomyelitis herpes, Merkel cell polyomavirus infection, Mesenteric abscess, Metagonimiasis, Metapneumovirus bronchiolitis, Metapneumovirus infection, Metapneumovirus pneumonia, Methylobacterium infection, Micrococcal sepsis, Micrococcus infection, Microsporidia infection, Microsporum infection, Middle East respiratory syndrome, Miliary pneumonia, Milker's nodules, Molluscum contagiosum, Monkeypox, Mononucleosis syndrome, Moraxella infection, Morganella infection, Mucocutaneous candidiasis, Mucocutaneous leishmaniasis, Mucormycosis, Mucosal infection, Multisystem inflammatory syndrome, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome in children, Mumps, Mumps deafness, Murine typhus, Murray Valley encephalitis, Muscle abscess, Mycetoma mycotic, Mycobacterial disease carrier, Mycobacterial infection, Mycobacterial peritonitis, Mycobacterium abscessus infection, Mycobacterium avium complex immune restoration disease, Mycobacterium avium complex infection, Mycobacterium chelonae infection, Mycobacterium fortuitum infection, Mycobacterium haemophilum infection, Mycobacterium kansasii infection, Mycobacterium marinum infection, Mycobacterium ulcerans infection, Mycoplasma genitalium infection, Mycoplasma infection, Mycoplasmal postabortal fever, Mycoplasmal postpartum fever, Mycotic corneal ulcer, Mycotic endophthalmitis, Mycotoxicosis, Myelitis, Myiasis, Myocardiac abscess, Myocarditis bacterial, Myocarditis helminthic, Myocarditis infectious, Myocarditis meningococcal, Myocarditis mycotic, Myocarditis post infection, Myocarditis septic, Myocarditis syphilitic, Myocarditis toxoplasmal, Myometritis, Myringitis, Naegleria infection, Nail bed infection, Nail bed infection bacterial, Nail bed infection viral, Nail candida, Nail infection, Nasal abscess, Nasal candidiasis, Nasal herpes, Nasal vestibulitis, Nasopharyngitis, Necrobacillosis, Necrotising fasciitis, Necrotising fasciitis fungal, Necrotising fasciitis staphylococcal, Necrotising fasciitis streptococcal, Necrotising herpetic retinopathy, Necrotising soft tissue infection, Necrotising ulcerative gingivostomatitis, Necrotising ulcerative periodontitis, Neisseria infection, Nematodiasis, Neonatal bacteraemia, Neonatal bacterial pneumonia, Neonatal candida infection, Neonatal infection, Neonatal infective mastitis, Neonatal mucocutaneous herpes simplex, Neonatal pneumonia, Neoscytalidium infection, Neovaginal infection, Nephritis bacterial, Neuroborreliosis, Neurocryptococcosis, Neurocysticercosis, Neurohydatidosis, Neurological infection, Neurosyphilis, Neutropenic infection, Neutropenic sepsis, Newcastle disease, Nipah virus infection, Nipple infection, Nocardia sepsis, Nocardiosis, Norovirus infection, North Asian tick typhus, Nosocomial infection, O'nyong-nyong fever, Obstetric infection, Obstetrical tetanus, Ocular vaccinia virus infection, Oculoglandular syndrome, Oesophageal abscess, Oesophageal candidiasis, Oesophageal infection, Oesophageal tuberculosis, Oesophagitis bacterial, Omphalitis, Omsk haemorrhagic fever, Onchocerciasis, Onchodermatitis, Onychomycosis, Oophoritis, Ophthalmia neonatorum, Ophthalmic cysticercosis, Ophthalmic herpes simplex, Ophthalmic herpes zoster, Opisthorchiasis, Opportunistic infection, Optic neuritis meningococcal, Oral bacterial infection, Oral candidiasis, Oral fungal infection, Oral hairy leukoplakia, Oral helminthic infection, Oral herpes, Oral herpes zoster, Oral infection, Oral papilloma, Oral pustule, Oral tuberculosis, Oral viral infection, Orbital infection, Orbivirus infection, Orchitis, Orchitis mumps, Orf, Oro-pharyngeal aspergillosis, Oropharyngeal candidiasis, Oropharyngeal gonococcal infection, Oropharyngitis fungal, Oropouche fever, Orthopox virus infection, Osler's nodes, Osseous cryptococcosis, Osteoarticular sporotrichosis, Osteomyelitis, Osteomyelitis acute, Osteomyelitis bacterial, Osteomyelitis blastomyces, Osteomyelitis chronic, Osteomyelitis fungal, Osteomyelitis

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Safety Topic	Preferred Term
	salmonella, Osteomyelitis viral, Otitis externa, Otitis externa bacterial, Otitis externa candida, Otitis externa fungal, Otitis externa viral, Otitis media, Otitis media acute, Otitis media bacterial, Otitis media chronic, Otitis media fungal, Otitis media haemophilus, Otitis media moraxella, Otitis media pneumococcal, Otitis media post measles, Otitis media staphylococcal, Otitis media viral, Otosalpingitis, Ovarian abscess, Ovarian bacterial infection, Overgrowth bacterial, Overgrowth fungal, Overgrowth of nonsusceptible organisms, Paediatric acute-onset neuropsychiatric syndrome, Pancreas infection, Pancreatic abscess, Pancreatitis bacterial, Pancreatitis fungal, Pancreatitis helminthic, Pancreatitis mumps, Pancreatitis viral, Panencephalitis, Pantoea agglomerans infection, Papilloma viral infection, Papillon-Lefevre syndrome, Papular pruritic eruption of HIV, Paracancerous pneumonia, Paracoccidioides infection, Paragonimiasis, Parainfluenzae viral bronchitis, Parainfluenzae viral laryngotracheobronchitis, Parainfluenzae virus infection, Parametric abscess, Parametritis, Paranasal mucopyocoele, Paranasal sinus abscess, Parapharyngeal space infection, Parapox virus infection, Parasite allergy, Parasitic encephalitis, Parasitic gastroenteritis, Parasitic oesophagitis, Parasitic pneumonia, Paraspinal abscess, Parathyroid gland abscess, Paratyphoid fever, Paravaccinia, Parechovirus infection, Paronychia, Parotid abscess, Parotitis, Parvimonas infection, Parvimonas micra infection, Parvovirus B19 infection, Parvovirus B19 infection reactivation, Parvovirus infection, Pasteurella infection, Pathogen resistance, Pelvic abscess, Pelvic infection, Pelvic inflammatory disease, Pelvic inflammatory disease mycoplasmal, Pelvic sepsis, Penicillium infection, Penile abscess, Penile gangrene, Penile infection, Penile wart, Peptic ulcer helicobacter, Peptostreptococcus infection, Peri-implantitis, Perianal streptococcal infection, Pericarditis amoebic, Pericarditis fungal, Pericarditis gonococcal, Pericarditis helminthic, Pericarditis histoplasma, Pericarditis infective, Pericarditis meningococcal, Pericarditis mycoplasmal, Pericarditis rheumatic, Pericarditis syphilitic, Pericarditis tuberculous, Perichondritis, Pericoronitis, Perihepatic abscess, Perihepatitis, Perihepatitis gonococcal, Perinatal HBV infection, Perinatal HIV infection, Perineal abscess, Perineal cellulitis, Perineal infection, Perinephric abscess, Perinephritis, Periodontal destruction, Periodontic-endodontic disease, Periodontitis, Periorbital abscess, Periorbital cellulitis, Periorbital infection, Peripheral nerve infection, Periporitis staphylogenes, Perirectal abscess, Peritoneal abscess, Peritoneal candidiasis, Peritoneal chlamydia infection, Peritoneal tuberculosis, Peritonitis, Peritonitis bacterial, Peritonitis gonococcal, Peritonitis helminthic, Peritonitis pneumococcal, Peritonitis syphilitic, Peritonitis viral, Peritonsillar abscess, Peritonsillitis, Periumbilical abscess, Persistent generalised lymphadenopathy, Pertussis, Pertussis-like syndrome, Peruvian wart, Petrositis, Phaeohyphomycosis, Phaeohyphomycotic brain abscess, Pharyngeal abscess, Pharyngeal chlamydia infection, Pharyngeal pustule, Pharyngitis, Pharyngitis bacterial, Pharyngitis mycoplasmal, Pharyngitis streptococcal, Pharyngoconjunctival fever of children, Pharyngolaryngeal abscess, Pharyngotonsillitis, Phlebitis infective, Phlebotomus fever, Phlyctenular keratoconjunctivitis, Picornavirus infection, Pilonidal cyst congenital, Pilonidal disease, Pinta, Pitted keratolysis, Plague, Plague sepsis, Plasmodium falciparum infection, Plasmodium knowlesi infection, Plasmodium malariae infection, Plasmodium ovale infection, Plasmodium vivax infection, Plesiomonas shigelloides infection, Pleural infection, Pleural infection bacterial, Pleurisy bacterial, Pleurisy viral, Pneumococcal bacteraemia, Pneumococcal infection, Pneumococcal sepsis, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia acinetobacter, Pneumonia adenoviral, Pneumonia anthrax, Pneumonia aspiration, Pneumonia bacterial, Pneumonia bordetella, Pneumonia chlamydial, Pneumonia cryptococcal, Pneumonia cytomegaloviral, Pneumonia escherichia, Pneumonia fungal, Pneumonia haemophilus, Pneumonia helminthic, Pneumonia herpes viral, Pneumonia influenzal, Pneumonia klebsiella, Pneumonia legionella, Pneumonia measles, Pneumonia moraxella, Pneumonia mycoplasmal, Pneumonia necrotising, Pneumonia parainfluenzae viral, Pneumonia pneumococcal, Pneumonia proteus, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia salmonella, Pneumonia serratia, Pneumonia staphylococcal, Pneumonia streptococcal, Pneumonia toxoplasmal, Pneumonia tularaemia, Pneumonia viral, Pneumonic plague, Pogosta disease, Polioencephalitis, Poliomyelitis, Polyneuropathy mumps, Polyomavirus viraemia, Polyomavirus-associated nephropathy, Poncet's disease, Pontiac fever, Porphyromonas bacteraemia, Porphyromonas infection, Portal pyaemia, Post abortion infection, Post herpetic neuralgia, Post infection glomerulonephritis, Post measles blindness, Post polio syndrome, Post procedural cellulitis, Post procedural infection, Post procedural meningitis, Post procedural pneumonia, Post procedural sepsis, Post streptococcal glomerulonephritis, Post transplant lymphoproliferative disorder, Post treatment Lyme disease syndrome, Post vaccination

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Safety Topic	Preferred Term
	autoinoculation, Post-acute COVID-19 syndrome, Postoperative abscess, Postoperative wound infection, Postpartum sepsis, Pouchitis infective, Pregnancy related infection, Presumed ocular histoplasmosis syndrome, Primary syphilis, Primary transmission, Prion disease, Proctitis bacterial, Proctitis chlamydial, Proctitis fungal, Proctitis gonococcal, Proctitis herpes, Proctitis monilial, Proctitis mycoplasmal, Proctitis viral, Progressive massive fibrosis, Progressive multifocal leukoencephalopathy, Progressive vaccinia, Prostate infection, Prostatic abscess, Prostatitis Escherichia coli, Prostatitis gonococcal, Prostatitis trichomonal, Prostatitis tuberculous, Prosthetic valve endocarditis, Proteus infection, Protothecosis, Protozoal corneal ulcer, Providencia infection, Providencia urinary tract infection, Pseudallescheria infection, Pseudallescheria sepsis, Pseudoaneurysm infection, Pseudomembranous colitis, Pseudomonal bacteraemia, Pseudomonal sepsis, Pseudomonal skin infection, Pseudomonas aeruginosa meningitis, Pseudomonas bronchitis, Pseudomonas infection, Pseudomonas peritonitis, Psittacosis, Psoas abscess, Psorospermiasis, Puerperal infection, Puerperal pyrexia, Pulmonary blastomycosis, Pulmonary echinococciasis, Pulmonary gangrene, Pulmonary histoplasmosis, Pulmonary mucormycosis, Pulmonary nocardiosis, Pulmonary paracoccidioidomycosis, Pulmonary sepsis, Pulmonary sporotrichosis, Pulmonary syphilis, Pulmonary trichosporonosis, Pulmonary tuberculoma, Pulmonary tuberculosis, Pulpitis dental, Puncture site abscess, Puncture site cellulitis, Puncture site infection, Purple urine bag syndrome, Purulence, Purulent discharge, Purulent pericarditis, Purulent synovitis, Pustule, Pyelitis, Pyelocystitis, Pyelonephritis, Pyelonephritis acute, Pyelonephritis chronic, Pyelonephritis fungal, Pyelonephritis mycoplasmal, Pyelonephritis viral, Pyloric abscess, Pyoderma, Pyoderma streptococcal, Pyometra, Pyomyositis, Pyonephrosis, Pyopneumothorax, Pyospermia, Pythium insidiosum infection, Pyuria, Q fever, Queensland tick typhus, Rabies, Radiation site infection, Raoultella ornithinolytica infection, Rash pustular, Recrudescent typhus, Rectal abscess, Rectovaginal septum abscess, Recurrent pyogenic cholangitis, Recurrent subareolar breast abscess, Relapsing fever, Renal abscess, Renal cyst infection, Renal echinococciasis, Renal graft infection, Renal syphilis, Renal tuberculosis, Reoviral infection, Reproductive tract procedural infection, Respiratory moniliasis, Respiratory papilloma, Respiratory syncytial virus bronchiolitis, Respiratory syncytial virus bronchitis, Respiratory syncytial virus infection, Respiratory tract chlamydial infection, Respiratory tract infection, Respiratory tract infection bacterial, Respiratory tract infection fungal, Respiratory tract infection viral, Retinitis, Retinitis histoplasma, Retinitis viral, Retroperitoneal abscess, Retroperitoneal infection, Retroperitonitis, Retroviral infection, Retroviral rebound syndrome, Reye's syndrome, Rheumatic fever, Rheumatic heart disease, Rhinitis, Rhinocerebral mucormycosis, Rhinolaryngitis, Rhinoscleroma, Rhinosporidiosis, Rhinotracheitis, Rhinovirus infection, Rhizobium radiobacter bacteraemia, Rhodococcus infection, Rickettsialpox, Rickettsioses not tick borne, Rickettsiosis, Rift Valley fever, Rocio virus infection, Rocky mountain spotted fever, Romana's sign, Root canal infection, Roseola, Rotavirus infection, Rubella, Rubella in pregnancy, Rubella infection neurological, SARS-CoV-2 carrier, SARS-CoV-2 sepsis, SARS-CoV-2 viraemia, SJS-TEN overlap, Salmonella bacteraemia, Salmonella sepsis, Salmonellosis, Salpingitis, Salpingitis gonococcal, Salpingitis tuberculous, Salpingo-oophoritis, Sapovirus infection, Sarcocystis infection, Scarlet fever, Scedosporium infection, Schistosomiasis, Schistosomiasis bladder, Schistosomiasis cutaneous, Schistosomiasis liver, Scleroedema, Scopulariopsis infection, Scrotal abscess, Scrotal cellulitis, Scrotal gangrene, Scrotal infection, Scrub typhus, Sebaceous gland infection, Secondary amyloidosis, Secondary syphilis, Secondary transmission, Seminal vesicle abscess, Seminal vesicular infection, Seminal vesiculitis gonococcal, Sepsis, Sepsis neonatal, Sepsis pasteurella, Sepsis syndrome, Septic arthritis haemophilus, Septic arthritis neisserial, Septic arthritis staphylococcal, Septic arthritis streptobacillus, Septic arthritis streptococcal, Septic cardiomyopathy, Septic cerebral embolism, Septic coagulopathy, Septic embolus, Septic encephalopathy, Septic endocarditis, Septic necrosis, Septic phlebitis, Septic pulmonary embolism, Septic rash, Septic shock, Septic vasculitis, Serratia bacteraemia, Serratia infection, Serratia sepsis, Severe acute respiratory syndrome, Severe asthma with fungal sensitisation, Severe cutaneous adverse reaction, Severe fever with thrombocytopenia syndrome, Severe invasive streptococcal infection, Sexual transmission of infection, Sexually transmitted disease, Sexually transmitted disease carrier, Shewanella algae bacteraemia, Shigella infection, Shigella sepsis, Shunt infection, Sialoadenitis, Silicotuberculosis, Sinobronchitis, Sinonasal papilloma, Sinusitis, Sinusitis aspergillus, Sinusitis bacterial, Sinusitis fungal, Skin bacterial infection, Skin candida, Skin graft infection, Skin infection, Skin infection helminthic, Skin papilloma, Slow virus infection, Small intestine gangrene, Smallpox, Snowshoe hare virus infection, Soft tissue infection, Southern tick-associated rash illness, Spermatic cord funiculitis, Sphingomonas

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Safety Topic	Preferred Term
	paucimobilis bacteraemia, Sphingomonas paucimobilis infection, Spinal cord abscess, Spinal cord infection, Spinal empyema, Spirillary fever, Spirochaetal infection, Spleen tuberculosis, Splenic abscess, Splenic candidiasis, Splenic infection, Splenic infection bacterial, Splenic infection fungal, Splenic infection helminthic, Splenic infection viral, Spontaneous bacterial peritonitis, Sporadic infantile bilateral striatal necrosis, Sporotrichosis, Sputum purulent, St. Louis encephalitis, Staphylococcal abscess, Staphylococcal bacteraemia, Staphylococcal blepharitis, Staphylococcal impetigo, Staphylococcal infection, Staphylococcal mediastinitis, Staphylococcal osteomyelitis, Staphylococcal parotitis, Staphylococcal pharyngitis, Staphylococcal scalded skin syndrome, Staphylococcal sepsis, Staphylococcal skin infection, Staphylococcal toxaemia, Stenotrophomonas bacteraemia, Stenotrophomonas infection, Stenotrophomonas maltophilia pneumonia, Stenotrophomonas sepsis, Sternitis, Stevens-Johnson syndrome, Stitch abscess, Stoma site abscess, Stoma site candida, Stoma site cellulitis, Stoma site infection, Stomatococcal infection, Streptobacillary fever, Streptobacillus infection, Streptococcal abscess, Streptococcal bacteraemia, Streptococcal bronchitis, Streptococcal endocarditis, Streptococcal impetigo, Streptococcal infection, Streptococcal sepsis, Streptococcal urinary tract infection, Strongyloidiasis, Stump appendicitis, Subacute endocarditis, Subacute inflammatory demyelinating polyneuropathy, Subacute sclerosing panencephalitis, Subarachnoid abscess, Subcutaneous abscess, Subdiaphragmatic abscess, Subdural abscess, Subgaleal abscess, Subglottic laryngitis, Submandibular abscess, Subperiosteal abscess, Subungual abscess, Superinfection, Superinfection bacterial, Superinfection fungal, Superinfection mycobacterial, Superinfection viral, Suspected COVID-19, Suspected transmission of an infectious agent via product, Sweat gland infection, Sweating fever, Sydenham's chorea, Syngamiasis, Syphilis, Syphilis anal, Syphilis genital, Syphilis musculoskeletal, Syphilitic endocarditis of heart valve, Syphilitic pelvic inflammatory disease, Systemic bacterial infection, Systemic bartonellosis, Systemic candida, Systemic infection, Systemic mycosis, Systemic viral infection, T-cell lymphoma, T-cell type acute leukaemia, TORCH infection, Taeniasis, Tertiary syphilis, Testicular abscess, Tetanus, Tetanus neonatorum, Thrombophlebitis septic, Thymus abscess, Thyroglossal cyst infection, Thyroid echinococciasis, Thyroid gland abscess, Thyroid tuberculosis, Thyroiditis subacute, Tick paralysis, Tick-borne fever, Tick-borne viral encephalitis, Tinea barbae, Tinea blanca, Tinea capitis, Tinea cruris, Tinea faciei, Tinea imbricata, Tinea infection, Tinea manuum, Tinea nigra, Tinea pedis, Tinea versicolour, Tongue abscess, Tongue fungal infection, Tonsil squamous cell papilloma, Tonsillitis, Tonsillitis bacterial, Tonsillitis fungal, Tonsillitis streptococcal, Tooth abscess, Tooth infection, Tornwaldt bursitis, Torulopsis infection, Toxic epidermal necrolysis, Toxic shock syndrome, Toxic shock syndrome staphylococcal, Toxic shock syndrome streptococcal, Toxocariasis, Toxoplasmosis, Tracheal abscess, Tracheal papilloma, Tracheitis, Tracheitis obstructive, Tracheobronchitis, Tracheobronchitis bacterial, Tracheobronchitis mycoplasmal, Tracheobronchitis viral, Tracheostomy infection, Trachoma, Transmission of an infectious agent via product, Transmission of an infectious agent via transplant, Transplant abscess, Trematode infection, Trench fever, Trichiniasis, Trichomoniasis, Trichomoniasis intestinal, Trichophytic granuloma, Trichophytosis, Trichosporon infection, Trichostrongyliasis, Trichuriasis, Trombidiasis, Tropical eosinophilia, Tropical infectious disease, Tropical spastic paresis, Tropical ulcer, Trypanosomiasis, Tuberculoid leprosy, Tuberculoma, Tuberculoma of central nervous system, Tuberculosis, Tuberculosis bladder, Tuberculosis gastrointestinal, Tuberculosis liver, Tuberculosis of central nervous system, Tuberculosis of eye, Tuberculosis of genitourinary system, Tuberculosis of intrathoracic lymph nodes, Tuberculosis of peripheral lymph nodes, Tuberculosis of uterine cervix, Tuberculosis ureter, Tuberculous abscess central nervous system, Tuberculous endometritis, Tuberculous laryngitis, Tuberculous pelvic inflammatory disease, Tuberculous pleurisy, Tuberculous tenosynovitis, Tubo-ovarian abscess, Tularaemia, Tungiasis, Type 1 lepra reaction, Type 2 lepra reaction, Typhoid carrier, Typhoid fever, Typhus, Umbilical hernia gangrenous, Umbilical sepsis, Upper aerodigestive tract infection, Upper respiratory fungal infection, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Upper respiratory tract infection helminthic, Urachal sinus infection, Ureaplasma cervicitis, Ureaplasma infection, Ureaplasmal vulvovaginitis, Ureter abscess, Ureteritis, Urethral abscess, Urethral carbuncle, Urethral discharge syndrome, Urethral papilloma, Urethral stricture post infection, Urethritis, Urethritis chlamydial, Urethritis gonococcal, Urethritis mycoplasmal, Urethritis trichomonal, Urethritis ureaplasmal, Urinary bladder abscess, Urinary meatitis, Urinary tract abscess, Urinary tract candidiasis, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal, Urinary tract infection fungal, Urinary tract infection neonatal, Urinary tract infection

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Safety Topic	Preferred Term
	pseudomonal, Urinary tract infection staphylococcal, Urinary tract infection viral, Urogenital infection bacterial, Urogenital infection fungal, Urogenital trichomoniasis, Urosepsis, Uterine abscess, Uterine infection, Vaccination site abscess, Vaccination site cellulitis, Vaccination site infection, Vaccination site joint infection, Vaccination site pustule, Vaccine associated paralytic poliomyelitis, Vaccine bacteria shedding, Vaccine breakthrough infection, Vaccine derived SARS-CoV-2 infection, Vaccine virus shedding, Vaccinia virus infection, Vaginal abscess, Vaginal cellulitis, Vaginal infection, Vaginitis chlamydial, Vaginitis gardnerella, Vaginitis viral, Variant Creutzfeldt-Jakob disease, Varicella, Varicella encephalitis, Varicella keratitis, Varicella meningitis, Varicella post vaccine, Varicella zoster gastritis, Varicella zoster oesophagitis, Varicella zoster pneumonia, Varicella zoster sepsis, Varicella zoster viraemia, Varicella zoster virus infection, Vascular access site abscess, Vascular access site cellulitis, Vascular access site infection, Vascular device infection, Vascular graft infection, Vector-borne transmission of infection, Veillonella infection, Vertical infection transmission, Vessel puncture site cellulitis, Vessel puncture site infection, Vestibular neuronitis, Vestibulitis, Vibrio vulnificus infection, Viraemia, Viral abdominal infection, Viral acanthoma, Viral cardiomyopathy, Viral corneal ulcer, Viral diarrhoea, Viral disease carrier, Viral epiglottitis, Viral haemorrhagic cystitis, Viral hepatitis carrier, Viral infection, Viral keratouveitis, Viral labyrinthitis, Viral mastitis, Viral myelitis, Viral myocarditis, Viral myositis, Viral oesophagitis, Viral parotitis, Viral pericarditis, Viral pharyngitis, Viral rash, Viral rhinitis, Viral sepsis, Viral sinusitis, Viral skin infection, Viral tonsillitis, Viral tracheitis, Viral upper respiratory tract infection, Viral uveitis, Viral vasculitis, Viral vector shedding, Virologic failure, Viruria, Visceral larva migrans, Visceral leishmaniasis, Vitreous abscess, Vitritis infective, Vorticella infection, Vulval abscess, Vulval cellulitis, Vulvitis, Vulvovaginal candidiasis, Vulvovaginal human papilloma virus infection, Vulvovaginal mycotic infection, Vulvovaginal warts, Vulvovaginitis, Vulvovaginitis chlamydial, Vulvovaginitis gonococcal, Vulvovaginitis helminthic, Vulvovaginitis staphylococcal, Vulvovaginitis streptococcal, Vulvovaginitis trichomonal, WU virus infection, Waterhouse-Friderichsen syndrome, Weil's disease, Weissella infection, West Nile viral infection, Whipple's disease, Withdrawal hepatitis, Wound abscess, Wound cellulitis, Wound infection, Wound infection bacterial, Wound infection fungal, Wound infection helminthic, Wound infection pseudomonas, Wound infection staphylococcal, Wound infection viral, Wound sepsis, X-linked lymphoproliferative syndrome, Yaws, Yaws of bone, Yaws of skin, Yellow fever, Yellow fever vaccine-associated neurotropic disease, Yellow fever vaccine-associated viscerotropic disease, Yersinia bacteraemia, Yersinia infection, Yersinia meningitis, Yersinia sepsis, Young's syndrome, Zika virus associated Guillain Barre syndrome, Zika virus associated birth defect, Zika virus associated microencephaly, Zika virus associated ocular birth defect, Zika virus infection, Zoonosis, Zoonotic bacterial infection, Zygomatic abscess
Myelosuppression - Anaemia	Anaemia, Anaemia macrocytic, Anaemia neonatal, Aplasia pure red cell, Aplastic anaemia, Erythroblast count abnormal, Erythroblast count decreased, Erythroid dysplasia, Erythroid maturation arrest, Erythropenia, Erythropoiesis abnormal, Foetal anaemia, Haematocrit abnormal, Haematocrit decreased, Haemoglobin abnormal, Haemoglobin decreased, Hypoplastic anaemia, Leukoerythroblastic anaemia, Microcytic anaemia, Normochromic anaemia, Normochromic normocytic anaemia, Normocytic anaemia, Proerythroblast count abnormal, Proerythroblast count decreased, Red blood cell count abnormal, Red blood cell count decreased, Reticulocyte count abnormal, Reticulocyte count decreased, Reticulocyte percentage decreased, Reticulocytopenia
Myelosuppression - Leukopenia	B-lymphocyte count abnormal, B-lymphocyte count decreased, CD4 lymphocyte percentage decreased, CD4 lymphocytes abnormal, CD4 lymphocytes decreased, CD4/CD8 ratio decreased, CD8 lymphocyte percentage decreased, CD8 lymphocytes abnormal, CD8 lymphocytes decreased, Idiopathic CD4 lymphocytopenia, Leukopenia, Lymphocyte count abnormal, Lymphocyte count decreased, Lymphocyte percentage abnormal, Lymphocyte percentage decreased, Lymphopenia, T-lymphocyte count abnormal, T-lymphocyte count decreased, White blood cell count abnormal, White blood cell count decreased, White blood cell disorder
Myelosuppression - Neutropenia	Agranulocytosis, Autoimmune neutropenia, Benign ethnic neutropenia, Cyclic neutropenia, Febrile neutropenia, Felty's syndrome, Granulocytopenia, Granulocytopenia neonatal, Idiopathic neutropenia, Infantile genetic agranulocytosis, Neutropenia, Neutropenia neonatal, Neutropenic colitis, Neutropenic infection, Neutropenic sepsis, Neutrophil count decreased, Radiation neutropenia, Transfusion-related alloimmune neutropenia
Myelosuppression - Other	Aplastic anaemia, Autoimmune aplastic anaemia, Bicytopenia, Bone marrow failure, Cytopenia, Febrile bone marrow aplasia, Full blood count decreased, Gelatinous transformation of the bone marrow,

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Safety Topic	Preferred Term
	Immune-mediated cytopenia, Immune-mediated pancytopenia, Myelosuppression, Pancytopenia, Panmyelopathy
Myelosuppression - Thrombocytopenia	Acquired amegakaryocytic thrombocytopenia, Immature platelet fraction decreased, Megakaryocytes abnormal, Megakaryocytes decreased, Platelet count abnormal, Platelet count decreased, Platelet disorder, Platelet maturation arrest, Platelet production decreased, Platelet toxicity, Plateletcrit abnormal, Plateletcrit decreased, Radiation thrombocytopenia, Thrombocytopenia, Thrombocytopenia neonatal
Myelosuppression - Thrombocytopenia related bleeding events	Abdominal wall haematoma, Abdominal wall haemorrhage, Abnormal clotting factor, Abnormal menstrual clots, Abnormal uterine bleeding, Abnormal withdrawal bleeding, Achenbach syndrome, Acquired Von Willebrand's disease, Acquired dysfibrinogenaemia, Acquired factor IX deficiency, Acquired factor V deficiency, Acquired factor VIII deficiency, Acquired factor XI deficiency, Acquired haemophilia, Activated partial thromboplastin time abnormal, Activated partial thromboplastin time prolonged, Activated partial thromboplastin time ratio abnormal, Activated partial thromboplastin time ratio fluctuation, Activated partial thromboplastin time ratio increased, Acute haemorrhagic leukoencephalitis, Acute haemorrhagic ulcerative colitis, Administration site bruise, Administration site haematoma, Administration site haemorrhage, Adrenal haematoma, Adrenal haemorrhage, Anal fissure haemorrhage, Anal haemorrhage, Anal ulcer haemorrhage, Anastomotic haemorrhage, Anastomotic ulcer haemorrhage, Aneurysm ruptured, Angina bullosa haemorrhagica, Anorectal varices haemorrhage, Anti factor IX antibody positive, Anti factor V antibody positive, Anti factor VII antibody positive, Anti factor VIII antibody positive, Anti factor X activity abnormal, Anti factor X activity increased, Anti factor X antibody positive, Anti factor XI antibody positive, Anti factor XII antibody positive, Anticoagulant-related nephropathy, Antiplatelet reversal therapy, Antithrombin III abnormal, Antithrombin III increased, Aortic aneurysm rupture, Aortic dissection rupture, Aortic intramural haematoma, Aortic perforation, Aortic rupture, Aponeurosis contusion, Application site bruise, Application site haematoma, Application site haemorrhage, Application site purpura, Arterial haemorrhage, Arterial intramural haematoma, Arterial perforation, Arterial rupture, Arteriovenous fistula site haematoma, Arteriovenous fistula site haemorrhage, Arteriovenous graft site haematoma, Arteriovenous graft site haemorrhage, Astringent therapy, Atrial rupture, Auricular haematoma, Basal ganglia haematoma, Basal ganglia haemorrhage, Basilar artery perforation, Bladder tamponade, Bleeding time abnormal, Bleeding time prolonged, Bleeding varicose vein, Blood blister, Blood fibrinogen abnormal, Blood fibrinogen decreased, Blood loss anaemia, Blood thrombin abnormal, Blood thrombin decreased, Blood thromboplastin abnormal, Blood thromboplastin decreased, Blood urine, Blood urine present, Bloody discharge, Bloody peritoneal effluent, Bone contusion, Bone marrow haemorrhage, Brain contusion, Brain stem haematoma, Brain stem haemorrhage, Brain stem microhaemorrhage, Breast haematoma, Breast haemorrhage, Broad ligament haematoma, Bronchial haemorrhage, Bronchial varices haemorrhage, Bullous haemorrhagic dermatosis, Bursal haematoma, Capillary fragility abnormal, Capillary fragility increased, Capillary permeability increased, Cardiac contusion, Carotid aneurysm rupture, Carotid artery perforation, Carotid blowout syndrome, Catheter site bruise, Catheter site haematoma, Catheter site haemorrhage, Central nervous system haemorrhage, Cephalhaematoma, Cerebellar haematoma, Cerebellar haemorrhage, Cerebellar microhaemorrhage, Cerebral aneurysm perforation, Cerebral aneurysm ruptured syphilitic, Cerebral arteriovenous malformation haemorrhagic, Cerebral artery perforation, Cerebral cyst haemorrhage, Cerebral haematoma, Cerebral haemorrhage, Cerebral haemorrhage foetal, Cerebral haemorrhage neonatal, Cerebral microhaemorrhage, Cervix haematoma uterine, Cervix haemorrhage uterine, Chest wall haematoma, Choroidal haematoma, Choroidal haemorrhage, Chronic gastrointestinal bleeding, Chronic pigmented purpura, Ciliary body haemorrhage, Circulating anticoagulant, Clot retraction abnormal, Clot retraction time prolonged, Coagulation disorder neonatal, Coagulation factor IX level abnormal, Coagulation factor IX level decreased, Coagulation factor V level abnormal, Coagulation factor V level decreased, Coagulation factor VII level abnormal, Coagulation factor VII level decreased, Coagulation factor VIII level abnormal, Coagulation factor VIII level decreased, Coagulation factor X level abnormal, Coagulation factor X level decreased, Coagulation factor XI level abnormal, Coagulation factor XI level decreased, Coagulation factor XII level abnormal, Coagulation factor XII level decreased, Coagulation factor XIII level abnormal, Coagulation factor XIII level decreased, Coagulation factor decreased, Coagulation factor deficiency, Coagulation factor level abnormal, Coagulation time abnormal, Coagulation time prolonged, Coagulopathy, Coital bleeding, Colonic haematoma,

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Safety Topic	Preferred Term
	Conjunctival haemorrhage, Contusion, Corneal bleeding, Cullen's sign, Cystitis haemorrhagic, Deep dissecting haematoma, Diarrhoea haemorrhagic, Dilutional coagulopathy, Disseminated intravascular coagulation, Diverticulitis intestinal haemorrhagic, Diverticulum intestinal haemorrhagic, Duodenal ulcer haemorrhage, Duodenitis haemorrhagic, Ear haemorrhage, Ecchymosis, Encephalitis haemorrhagic, Enterocolitis haemorrhagic, Epidural haemorrhage, Epistaxis, Ethanol gelation test positive, Exsanguination, Extra-axial haemorrhage, Extradural haematoma, Extradural haematoma evacuation, Extravasation blood, Eye contusion, Eye haematoma, Eye haemorrhage, Eyelid bleeding, Eyelid contusion, Eyelid haematoma, Factor IX inhibition, Factor VIII activity abnormal, Factor VIII activity decreased, Factor VIII inhibition, Femoral artery perforation, Femoral vein perforation, Fibrin D dimer decreased, Fibrin D dimer increased, Fibrin abnormal, Fibrin decreased, Fibrin degradation products, Fibrin degradation products increased, Fibrinogen degradation products increased, Fibrinolysis abnormal, Fibrinolysis increased, Foetal-maternal haemorrhage, Fothergill sign positive, Gallbladder haematoma, Gastric haemorrhage, Gastric occult blood positive, Gastric ulcer haemorrhage, Gastric ulcer haemorrhage, obstructive, Gastric varices haemorrhage, Gastritis alcoholic haemorrhagic, Gastritis haemorrhagic, Gastroduodenal haemorrhage, Gastrointestinal anastomotic haemorrhage, Gastrointestinal haemorrhage, Gastrointestinal polyp haemorrhage, Gastrointestinal ulcer haemorrhage, Gastrointestinal vascular malformation haemorrhagic, Gastrooesophageal haemorrhage, Genital contusion, Genital haemorrhage, Gingival bleeding, Graft haemorrhage, Grey Turner's sign, Haemangioma rupture, Haemarthrosis, Haematemesis, Haematochezia, Haematocoele, Haematocrit abnormal, Haematocrit decreased, Haematoma, Haematoma evacuation, Haematoma infection, Haematoma muscle, Haematosalpinx, Haematospermia, Haematotympanum, Haematuria, Haematuria traumatic, Haemobilia, Haemoglobin abnormal, Haemoglobin decreased, Haemoperitoneum, Haemophilic arthropathy, Haemophilic pseudotumour, Haemoptysis, Haemorrhage, Haemorrhage coronary artery, Haemorrhage foetal, Haemorrhage in pregnancy, Haemorrhage intracranial, Haemorrhage neonatal, Haemorrhage subcutaneous, Haemorrhage subepidermal, Haemorrhage urinary tract, Haemorrhagic adrenal infarction, Haemorrhagic arteriovenous malformation, Haemorrhagic ascites, Haemorrhagic breast cyst, Haemorrhagic cerebellar infarction, Haemorrhagic cerebral infarction, Haemorrhagic cyst, Haemorrhagic diathesis, Haemorrhagic disease of newborn, Haemorrhagic disorder, Haemorrhagic erosive gastritis, Haemorrhagic gastroenteritis, Haemorrhagic hepatic cyst, Haemorrhagic infarction, Haemorrhagic intestinal infarction, Haemorrhagic necrotic pancreatitis, Haemorrhagic occlusive retinal vasculitis, Haemorrhagic ovarian cyst, Haemorrhagic stroke, Haemorrhagic thyroid cyst, Haemorrhagic transformation stroke, Haemorrhagic tumour necrosis, Haemorrhagic urticaria, Haemorrhagic vasculitis, Haemorrhoidal haemorrhage, Haemosiderin urine positive, Haemostasis, Haemothorax, Heavy menstrual bleeding, Henoch-Schonlein purpura, Hepatic artery haemorrhage, Hepatic haemangioma rupture, Hepatic haematoma, Hepatic haemorrhage, Hereditary haemorrhagic telangiectasia, Hyperfibrinolysis, Hypergammaglobulinaemic purpura of Waldenstrom, Hyphaema, Hypocoagulable state, Hypofibrinogenaemia, Hypoprothrombinaemia, Hypothrombinaemia, Hypothromboplastinaemia, ISTH score for disseminated intravascular coagulation, Iliac artery perforation, Iliac artery rupture, Iliac vein perforation, Immune thrombocytopenia, Implant site bruising, Implant site haematoma, Implant site haemorrhage, Incision site haematoma, Incision site haemorrhage, Increased tendency to bruise, Induced abortion haemorrhage, Inferior vena cava perforation, Infusion site bruising, Infusion site haematoma, Infusion site haemorrhage, Injection site bruising, Injection site haematoma, Injection site haemorrhage, Instillation site bruise, Instillation site haematoma, Instillation site haemorrhage, Intermenstrual bleeding, Internal haemorrhage, International normalised ratio abnormal, International normalised ratio increased, Intestinal haematoma, Intestinal haemorrhage, Intestinal varices haemorrhage, Intra-abdominal haematoma, Intra-abdominal haemorrhage, Intracerebral haematoma evacuation, Intracranial haematoma, Intracranial haemorrhage neonatal, Intracranial tumour haemorrhage, Intraocular haematoma, Intrapartum haemorrhage, Intratumoural haematoma, Intraventricular haemorrhage, Intraventricular haemorrhage neonatal, Iris haemorrhage, Joint microhaemorrhage, Jugular vein haemorrhage, Kidney contusion, Lacrimal haemorrhage, Large intestinal haemorrhage, Large intestinal ulcer haemorrhage, Laryngeal haematoma, Laryngeal haemorrhage, Lip haematoma, Lip haemorrhage, Liver contusion, Lower gastrointestinal haemorrhage, Lower limb artery perforation, Lymph node haemorrhage, Mallory-Weiss syndrome, Mediastinal haematoma, Mediastinal haemorrhage, Medical device site

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Safety Topic	Preferred Term
	bruise, Medical device site haematoma, Medical device site haemorrhage, Melaena, Melaena neonatal, Meningorrhagia, Menometrorrhagia, Menstrual clots, Mesenteric haematoma, Mesenteric haemorrhage, Mouth haemorrhage, Mucocutaneous haemorrhage, Mucosal haemorrhage, Muscle contusion, Muscle haemorrhage, Myocardial haemorrhage, Myocardial rupture, Naevus haemorrhage, Nail bed bleeding, Nasal septum haematoma, Neonatal gastrointestinal haemorrhage, Nephritis haemorrhagic, Nipple exudate bloody, Occult blood positive, Ocular retrobulbar haemorrhage, Oesophageal haemorrhage, Oesophageal intramural haematoma, Oesophageal ulcer haemorrhage, Oesophageal varices haemorrhage, Oesophagitis haemorrhagic, Omental haemorrhage, Optic disc haemorrhage, Optic nerve sheath haemorrhage, Oral blood blister, Oral contusion, Oral mucosa haematoma, Oral purpura, Orbital haematoma, Orbital haemorrhage, Osteorrhagia, Ovarian haematoma, Ovarian haemorrhage, Palpable purpura, Pancreatic haemorrhage, Pancreatic pseudocyst haemorrhage, Pancreatitis haemorrhagic, Papillary muscle haemorrhage, Paranasal sinus haematoma, Paranasal sinus haemorrhage, Parathyroid haemorrhage, Parotid gland haemorrhage, Pelvic haematoma, Pelvic haematoma obstetric, Pelvic haemorrhage, Penile contusion, Penile haematoma, Penile haemorrhage, Peptic ulcer haemorrhage, Pericardial haemorrhage, Perineal haematoma, Periorbital haematoma, Periorbital haemorrhage, Periosteal haematoma, Peripartum haemorrhage, Peripheral artery aneurysm rupture, Peripheral exudative haemorrhagic chorioretinopathy, Peripheral vascular haematoma, Peritoneal haematoma, Periventricular haemorrhage neonatal, Petechiae, Pharyngeal contusion, Pharyngeal haematoma, Pharyngeal haemorrhage, Pituitary apoplexy, Pituitary haemorrhage, Placenta praevia haemorrhage, Plasmin decreased, Plasmin increased, Plasmin inhibitor increased, Plasminogen activator inhibitor, Plasminogen activator inhibitor decreased, Plasminogen decreased, Plasminogen increased, Platelet factor 4 decreased, Polymenorrhagia, Post abortion haemorrhage, Post procedural contusion, Post procedural haematoma, Post procedural haematuria, Post procedural haemorrhage, Post transfusion purpura, Post-traumatic punctate intraepidermal haemorrhage, Postmenopausal haemorrhage, Postpartum haemorrhage, Prekallikrein increased, Premature separation of placenta, Procedural haemorrhage, Proctitis haemorrhagic, Prostatic haemorrhage, Protein C increased, Protein S abnormal, Protein S increased, Prothrombin fragment 1.2 increased, Prothrombin level abnormal, Prothrombin level decreased, Prothrombin time abnormal, Prothrombin time prolonged, Prothrombin time ratio abnormal, Prothrombin time ratio increased, Pulmonary alveolar haemorrhage, Pulmonary contusion, Pulmonary haematoma, Pulmonary haemorrhage, Pulmonary haemorrhage neonatal, Puncture site bruise, Puncture site haematoma, Puncture site haemorrhage, Purpura, Purpura fulminans, Purpura neonatal, Purpura non-thrombocytopenic, Purpura senile, Putamen haemorrhage, Radiation associated haemorrhage, Rectal haemorrhage, Rectal ulcer haemorrhage, Red blood cell count decreased, Renal artery perforation, Renal cyst haemorrhage, Renal haematoma, Renal haemorrhage, Respiratory tract haemorrhage, Respiratory tract haemorrhage neonatal, Reticulocyte count increased, Reticulocyte percentage abnormal, Reticulocyte percentage increased, Retinal aneurysm rupture, Retinal haemorrhage, Retinopathy haemorrhagic, Retroperitoneal haematoma, Retroperitoneal haemorrhage, Retroplacental haematoma, Ruptured cerebral aneurysm, Russell's viper venom time abnormal, Scalp haematoma, Scleral haematoma, Scleral haemorrhage, Scrotal haematocoele, Scrotal haematoma, Scrotal haemorrhage, Septic coagulopathy, Shock haemorrhagic, Skin haemorrhage, Skin neoplasm bleeding, Skin ulcer haemorrhage, Small intestinal haemorrhage, Small intestinal ulcer haemorrhage, Soft tissue haemorrhage, Spermatic cord haemorrhage, Spinal cord haematoma, Spinal cord haemorrhage, Spinal epidural haematoma, Spinal epidural haemorrhage, Spinal subarachnoid haemorrhage, Spinal subdural haematoma, Spinal subdural haemorrhage, Spleen contusion, Splenic artery perforation, Splenic haematoma, Splenic haemorrhage, Splenic varices haemorrhage, Splinter haemorrhages, Spontaneous haematoma, Spontaneous haemorrhage, Stoma site haemorrhage, Stomatitis haemorrhagic, Subarachnoid haematoma, Subarachnoid haemorrhage, Subarachnoid haemorrhage neonatal, Subcapsular hepatic haematoma, Subcapsular renal haematoma, Subcapsular splenic haematoma, Subchorionic haematoma, Subchorionic haemorrhage, Subclavian artery perforation, Subclavian vein perforation, Subcutaneous haematoma, Subdural haematoma, Subdural haematoma evacuation, Subdural haemorrhage, Subdural haemorrhage neonatal, Subendocardial haemorrhage, Subgaleal haematoma, Subgaleal haemorrhage, Subretinal haematoma, Superior vena cava perforation, Testicular haemorrhage, Thalamus haemorrhage, Third stage postpartum haemorrhage, Thoracic haemorrhage, Thrombin time abnormal, Thrombin time prolonged, Thrombin-antithrombin III complex

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Safety Topic	Preferred Term
	abnormal, Thrombin-antithrombin III complex increased, Thrombocytopenic purpura, Thrombomodulin increased, Thrombotic thrombocytopenic purpura, Thyroid haemorrhage, Tongue haematoma, Tongue haemorrhage, Tonsillar haemorrhage, Tooth pulp haemorrhage, Tooth socket haemorrhage, Tracheal haemorrhage, Traumatic haematoma, Traumatic haemorrhage, Traumatic haemothorax, Traumatic intracranial haematoma, Traumatic intracranial haemorrhage, Tumour haemorrhage, Ulcer haemorrhage, Umbilical cord haemorrhage, Umbilical haematoma, Umbilical haemorrhage, Unexpected vaginal bleeding on hormonal IUD, Upper gastrointestinal haemorrhage, Ureteric haemorrhage, Urethral haemorrhage, Urinary bladder haematoma, Urinary bladder haemorrhage, Urinary occult blood, Urinary occult blood positive, Urogenital haemorrhage, Uterine haematoma, Uterine haemorrhage, Vaccination site bruising, Vaccination site haematoma, Vaccination site haemorrhage, Vaginal haematoma, Vaginal haemorrhage, Varicose vein ruptured, Vascular access site bruising, Vascular access site haematoma, Vascular access site haemorrhage, Vascular access site rupture, Vascular anastomotic haemorrhage, Vascular graft haemorrhage, Vascular pseudoaneurysm ruptured, Vascular purpura, Vascular rupture, Vein rupture, Venous haemorrhage, Venous perforation, Ventricle rupture, Vertebral artery perforation, Vessel puncture site bruise, Vessel puncture site haematoma, Vessel puncture site haemorrhage, Vitreous haematoma, Vitreous haemorrhage, Vocal cord haemorrhage, Von Willebrand's factor antibody positive, Von Willebrand's factor multimers abnormal, Vulval haematoma, Vulval haematoma evacuation, Vulval haemorrhage, Withdrawal bleed, Wound haematoma, Wound haemorrhage
QT interval prolongation	Arrhythmic storm, Cardiac arrest, Cardiac death, Cardiac fibrillation, Cardio-respiratory arrest, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electrocardiogram U wave inversion, Electrocardiogram U wave present, Electrocardiogram U-wave abnormality, Electrocardiogram repolarisation abnormality, Long QT syndrome, Long QT syndrome congenital, Loss of consciousness, Seizure, Sudden cardiac death, Sudden death, Syncope, Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia
Renal toxicity	Acute kidney injury, Acute phosphate nephropathy, Albuminuria, Anuria, Azotaemia, Blood creatinine abnormal, Blood creatinine increased, Blood urea abnormal, Blood urea increased, Blood urea nitrogen/creatinine ratio increased, Continuous haemodiafiltration, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Creatinine urine abnormal, Creatinine urine decreased, Crystal nephropathy, Dialysis, Foetal renal impairment, Fractional excretion of sodium, Glomerular filtration rate abnormal, Glomerular filtration rate decreased, Haemodialysis, Haemofiltration, Hypercreatininaemia, Hyponatriuria, Intradialytic parenteral nutrition, Kidney injury molecule-1, Neonatal anuria, Nephritis, Nephropathy toxic, Neutrophil gelatinase-associated lipocalin increased, Oedema due to renal disease, Oliguria, Peritoneal dialysis, Prerenal failure, Protein urine present, Proteinuria, Renal failure, Renal failure neonatal, Renal function test abnormal, Renal impairment, Renal impairment neonatal, Renal transplant, Renal tubular disorder, Renal tubular dysfunction, Renal tubular injury, Renal tubular necrosis, Subacute kidney injury, Tubulointerstitial nephritis, Urea renal clearance decreased, Urine output decreased
Reproductive toxicity	11-beta-hydroxylase deficiency, 17,20-desmolase deficiency, 17-alpha-hydroxylase deficiency, 18q minus syndrome, 1p36 deletion syndrome, 2-Hydroxyglutaric aciduria, 20,22-desmolase deficiency, 21-hydroxylase deficiency, 22q11.2 deletion syndrome, 3-hydroxyacetyl-coenzyme A dehydrogenase deficiency, 3M syndrome, 5-alpha-reductase deficiency, ABO haemolytic disease of newborn, ABO incompatibility, ACAD9 deficiency, ADCY5-related dyskinesia, ADNP syndrome, ADSL gene mutation, AIDS dysmorphic syndrome, ALG8 gene mutation carrier, ASAH1 related disorder, ASXL1 gene mutation, Aase syndrome, Abdominal transposition, Abdominal wall anomaly, Aberrant aortic arch, Abetalipoproteinaemia, Ablepharon macrostomia syndrome, Abnormal DNA methylation, Abnormal cord insertion, Abnormal gene carrier, Abnormal labour, Abnormal labour affecting foetus, Abnormal palmar/plantar creases, Abnormal product of conception, Aborted pregnancy, Abortion, Abortion complete, Abortion complete complicated, Abortion complicated, Abortion early, Abortion incomplete, Abortion incomplete complicated, Abortion induced, Abortion induced complete, Abortion induced complete complicated, Abortion induced complicated, Abortion induced incomplete, Abortion induced incomplete complicated, Abortion infected, Abortion late, Abortion missed, Abortion of ectopic pregnancy, Abortion spontaneous, Abortion spontaneous complete, Abortion spontaneous complete complicated, Abortion spontaneous complicated, Abortion spontaneous incomplete, Abortion

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Safety Topic	Preferred Term
	spontaneous incomplete complicated, Abortion threatened, Acatalasaemia, Accessory auricle, Accessory breast, Accessory carpal bone, Accessory kidney, Accessory liver lobe, Accessory muscle, Accessory navicular syndrome, Accessory renal artery, Accessory salivary gland, Accessory spleen, Acetylcholinesterase deficiency, Achard Thiers syndrome, Achromotrichia congenital, Acne infantile, Acquired chromosomal abnormality, Acquired gene mutation, Acquired mitochondrial DNA deletion, Acquired mitochondrial DNA mutation, Acral peeling skin syndrome, Acrocallosal syndrome, Acrocephalosyndactyly, Acrodermatitis enteropathica, Acrodysostosis, Acrokeratosis verruciformis, Acromesomelic dysplasia, Acromicric dysplasia, Activated PI3 kinase delta syndrome, Acute fatty liver of pregnancy, Adactyly, Adams-Oliver syndrome, Adenine phosphoribosyl transferase deficiency, Adenomatous polyposis coli, Adenylosuccinate lyase deficiency, Administration site reaction neonatal, Adrenal insufficiency neonatal, Adrenocortical insufficiency neonatal, Adrenogenital syndrome, Adrenoleukodystrophy, Adult polyglucosan body disease, Afterbirth pain, Agitation neonatal, Aglossia, Aicardi's syndrome, Aicardi-Goutieres syndrome, Alagille syndrome, Albinism, Albright's disease, Alexander disease, Alkaptonuria, Allan-Herndon-Dudley syndrome, Alloimmunisation, Alpers disease, Alpha 1 foetoprotein abnormal, Alpha 1 foetoprotein amniotic fluid abnormal, Alpha 1 foetoprotein amniotic fluid decreased, Alpha 1 foetoprotein amniotic fluid increased, Alpha 1 foetoprotein amniotic fluid normal, Alpha 1 foetoprotein decreased, Alpha 1 foetoprotein increased, Alpha 1 foetoprotein normal, Alpha-1 antitrypsin deficiency, Alpha-1 antitrypsin deficiency carrier, Alpha-mannosidosis, Alpha-thalassaemia-intellectual deficit syndrome, Alport's syndrome, Alstroem syndrome, Alternating hemiplegia of childhood, Alveolar capillary dysplasia, Amastia, Amblyopia congenital, Amegakaryocytic thrombocytopenia, Aminoaciduria, Amniocentesis abnormal, Amniocentesis normal, Amniorrhexis, Amniorrhoea, Amnioscopy abnormal, Amnioscopy normal, Amniotic band syndrome, Amniotic cavity disorder, Amniotic cavity infection, Amniotic fluid erythropoietin level increased, Amniotic fluid index abnormal, Amniotic fluid index decreased, Amniotic fluid index increased, Amniotic fluid index normal, Amniotic fluid volume decreased, Amniotic fluid volume increased, Amniotic infection syndrome of Blane, Amniotic membrane rupture test positive, Ampullary renal pelvis, Amyotrophic lateral sclerosis gene carrier, Anaemia neonatal, Anaemia of pregnancy, Anaesthetic complication foetal, Anaesthetic complication neonatal, Anal atresia, Anaphylactoid syndrome of pregnancy, Anaplastic lymphoma kinase gene and nucleophosmin gene fusion overexpression, Anaplastic lymphoma kinase gene mutation, Andersen-Tawil syndrome, Androgen insensitivity syndrome, Androgen receptor gene overexpression, Anembryonic gestation, Anencephaly, Angelman's syndrome, Angiotensin II receptor type 1 antibody positive, Angiotensin converting enzyme inhibitor foetopathy, Aniridia, Aniridia-cerebellar ataxia-mental deficiency, Anisomelia, Annular pancreas, Anomalous arrangement of pancreaticobiliary duct, Anomalous pulmonary venous connection, Anomaly of external ear congenital, Anomaly of middle ear congenital, Anomaly of orbit, congenital, Anophthalmos, Anorchism, Anorectal agenesis, Anorectal malformation, Anotia, Anterior chamber cleavage syndrome, Anterior displaced anus, Antiphospholipid syndrome, Antithrombin III deficiency, Antley-Bixler syndrome, Aorta hypoplasia, Aortic valve atresia, Aorticopulmonary septal defect, Aorticopulmonary window repair, Apgar score abnormal, Apgar score low, Aphakia congenital, Aphallia, Aplasia, Aplasia cutis congenita, ApoB gene mutation, Apolipoprotein E e4 gene carrier, Apparent mineralocorticoid excess, Arachnodactyly, Arcuate foramen, Arginase deficiency, Argininosuccinate lyase deficiency, Argininosuccinate synthetase deficiency, Arhinencephaly, Arnold-Chiari malformation, Aromatic L-amino acid decarboxylase deficiency, Arrested labour, Arrhythmia neonatal, Arrhythmogenic right ventricular dysplasia, Arterial switch operation, Arterial tortuosity syndrome, Arteriovenous malformation, Artificial rupture of membranes, Ash leaf macule, Aspartate-glutamate-transporter deficiency, Aspartylglucosaminuria, Asphyxiating thoracic dystrophy, Asplenia, Assisted delivery, Asymmetric crying facies, Asymmetric thigh fold, Asymptomatic gene carrier, Asynclitic presentation, Ataxia telangiectasia, Ataxia with vitamin E deficiency, Atelectasis neonatal, Athelia, Atrial septal defect, Atrial septal defect repair, Atrial switch operation, Atrioventricular node dispersion, Atrioventricular septal defect, Auditory neuropathy spectrum disorder, Autoimmune lymphoproliferative syndrome, Autoinflammation with infantile enterocolitis, Autosomal chromosome anomaly, Autosomal recessive megaloblastic anaemia, Azygos lobe, BARD 1 gene mutation, BCOR gene mutation, BLyS polymorphism, BPES syndrome, BRAF gene mutation, BRCA1 gene mutation, BRCA2 gene mutation, Bacteriuria in pregnancy, Baller-Gerold syndrome, Balloon atrial septostomy, Baltic myoclonic epilepsy, Bannayan-Riley-Ruvalcaba syndrome, Baraitser Rodeck Garner syndrome, Barakat

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Safety Topic	Preferred Term
	syndrome, Barth syndrome, Bartter's syndrome, Basal cell naevus syndrome, Baseline foetal heart rate variability disorder, Beaver tail liver, Becker's muscular dystrophy, Beckwith-Wiedemann syndrome, Benign congenital hypotonia, Benign familial haematuria, Benign familial neonatal convulsions, Benign familial pemphigus, Benign hydatidiform mole, Benign macrocrania of infancy, Benign recurrent intrahepatic cholestasis, Benjamin syndrome, Berdon's syndrome, Bergmeister's papilla, Bernard-Soulier syndrome, Bertolotti's syndrome, Beta ketothiolase deficiency, Bicuspid aortic valve, Bicuspid pulmonary valve, Bifid ureter, Bile acid synthesis disorder, Biliary hamartoma, Bimanual uterine compression, Biochemical pregnancy, Biopsy chorionic villous abnormal, Biopsy foetal abnormal, Biopsy foetal normal, Biotinidase deficiency, Birt-Hogg-Dube syndrome, Birth defect correction, Birth mark, Birth trauma, Birth weight normal, Bladder agenesis, Blau syndrome, Blepharophimosis congenital, Blindness congenital, Bloch-Sulzberger syndrome, Block vertebra, Blood incompatibility haemolytic anaemia of newborn, Blood loss anaemia neonatal, Blood type incompatibility, Bloom syndrome, Bosch-Boonstra-Schaaf optic atrophy syndrome, Brachycephaly, Brachydactyly, Brachymetatarsia, Brachyolmia, Bradycardia foetal, Bradycardia neonatal, Brain malformation, Branchial cleft sinus, Branchial cyst, Branchio-oto-renal syndrome, Branchiogenic syndrome, Breast engorgement, Breast engorgement in newborn, Breast malformation, Breast milk substitute intolerance, Breech delivery, Breech extraction, Breech presentation, Brief psychotic disorder, with postpartum onset, Brief resolved unexplained event, Bronchial atresia, Bronchogenic cyst, Bronchopulmonary dysplasia, Brooke-Spiegler syndrome, Brow presentation, Brown-Vialetto-Van Laere syndrome, Brugada syndrome, Brunner syndrome, Bruton's agammaglobulinaemia, Bulbospinal muscular atrophy congenital, Buried penis syndrome, Butterfly vertebra, C-kit gene mutation, C-kit gene overexpression, CADASIL, CALR gene mutation, CANDLE syndrome, CARASIL syndrome, CARD9 deficiency, CBL gene mutation, CDKL5 deficiency disorder, CEBPA gene mutation, CEC syndrome, CFTR gene mutation, CHAPLE syndrome, CHARGE syndrome, CHILD syndrome, COPA syndrome, CRIA syndrome, CTLA4 deficiency, CYP1A2 polymorphism, CYP2B6 polymorphism, CYP2C19 polymorphism, CYP2C9 polymorphism, CYP2D6 polymorphism, CYP3A4 polymorphism, CYP3A5 polymorphism, Caesarean delivery on maternal request, Caesarean section, Campomelic syndrome, Camptodactyly congenital, Camptodactyly-arthropathy-coxa vara-pericarditis syndrome, Camptomelia, Canavan disease, Cancer gene carrier, Caput succedaneum, Carbamoyl phosphate synthetase deficiency, Carbohydrate metabolism disorder, Carbonic anhydrase gene mutation, Carcinogenic effect in offspring, Cardiac arrest neonatal, Cardiac lymphangioma, Cardiac malposition, Cardiac septal defect, Cardio-respiratory arrest neonatal, Cardiofaciocutaneous syndrome, Cardiomyopathy neonatal, Carney complex, Carnitine palmitoyltransferase deficiency, Carnitine-acylcarnitine translocase deficiency, Carpenter syndrome, Carpus curvus, Cartilage-hair hypoplasia, Cataract congenital, Catel Manzke syndrome, Caudal regression syndrome, Cayler cardiofacial syndrome, Central core disease, Central nervous system dermoid tumour, Cephalhaematoma, Cephalo-pelvic disproportion, Cerebellar dysplasia, Cerebellar hypoplasia, Cerebral arteriovenous malformation haemorrhagic, Cerebral atrophy congenital, Cerebral cavernous malformation, Cerebral dysgenesis, Cerebral folate deficiency, Cerebral haemorrhage foetal, Cerebral haemorrhage neonatal, Cerebral infarction foetal, Cerebral palsy, Cerebrocostomandibular syndrome, Cerebrohepatorenal syndrome, Cerebrovascular arteriovenous malformation, Cervical auricle, Cervical dilatation, Cervical incompetence, Cervix cerclage procedure, Cervix dystocia, Cervix scarring, Checkpoint kinase 2 gene mutation, Chediak-Higashi syndrome, Chiari network, Chimerism, Chloasma, Choanal atresia, Choanal stenosis, Cholangiectasis congenital, Cholestasis of pregnancy, Chondrodysplasia punctata, Chondroectodermal dysplasia, Chordee, Chorea-acanthocytosis, Chorioamniotic separation, Chorioretinal degeneration congenital, Choroidal coloboma, Chromosomal deletion, Chromosomal microduplication, Chromosomal mutation, Chronic atrial and intestinal dysrhythmia syndrome, Chronic granulomatous disease, Chronic infantile neurological cutaneous and articular syndrome, Chronic villitis of unknown etiology, Circulatory failure neonatal, Citrate transporter deficiency, Cleft lip, Cleft lip and palate, Cleft lip repair, Cleft palate, Cleft palate repair, Cleft uvula, Cleidocranial dysostosis, Clinodactyly, Cloacal exstrophy, Coagulation disorder neonatal, Coagulation factor mutation, Coarctation of the aorta, Cobb syndrome, Cochlear hypoplasia, Cockayne's syndrome, Coffin Siris syndrome, Coffin-Lowry syndrome, Cohen syndrome, Collodion baby, Coloboma, Colour blindness, Coma neonatal, Combined immunodeficiency, Complement deficiency disease, Complication of delivery, Complication of pregnancy, Cone dystrophy, Cone-rod dystrophy, Confined placental mosaicism, Congenital COVID-19, Congenital Chagas disease,

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Safety Topic	Preferred Term
	Congenital Ebola virus infection, Congenital Eustachian tube anomaly, Congenital HIV infection, Congenital Horner's syndrome, Congenital LUMBAR syndrome, Congenital Zika syndrome, Congenital abdominal hernia, Congenital absence of bile ducts, Congenital absence of cranial vault, Congenital absence of vertebra, Congenital acrochordon, Congenital adrenal gland hypoplasia, Congenital alopecia, Congenital amputation, Congenital anaemia, Congenital androgen deficiency, Congenital anisocoria, Congenital anomalies of ear ossicles, Congenital anomaly, Congenital anomaly in offspring, Congenital anomaly of adrenal gland, Congenital anomaly of inner ear, Congenital anosmia, Congenital aortic anomaly, Congenital aortic atresia, Congenital aortic dilatation, Congenital aortic stenosis, Congenital aortic valve incompetence, Congenital aortic valve stenosis, Congenital aplastic anaemia, Congenital aqueductal stenosis, Congenital arachnoid cyst, Congenital arterial malformation, Congenital arterial occlusion, Congenital arteriovenous fistula, Congenital astigmatism, Congenital aural fistula, Congenital benign neoplasm, Congenital bilateral perisylvian syndrome, Congenital bladder anomaly, Congenital bladder diverticulum, Congenital bladder neck obstruction, Congenital bowing of long bones, Congenital brain damage, Congenital bronchiectasis, Congenital bronchomalacia, Congenital calyceal diverticulum, Congenital cardiovascular anomaly, Congenital carnitine deficiency, Congenital central diabetes insipidus, Congenital central hypoventilation syndrome, Congenital central nervous system anomaly, Congenital cerebellar agenesis, Congenital cerebral cyst, Congenital cerebral haemangioma, Congenital cerebrovascular anomaly, Congenital choroid plexus cyst, Congenital choroidal anomaly, Congenital chylothorax, Congenital clavicular agenesis, Congenital claw toe, Congenital coagulopathy, Congenital condyloma, Congenital connective tissue disorder, Congenital corneal anomaly, Congenital coronary artery malformation, Congenital cranial dysinnervation disorder, Congenital cranial nerve paralysis, Congenital cutis laxa, Congenital cyst, Congenital cystic kidney disease, Congenital cytomegalovirus infection, Congenital deformity of clavicle, Congenital dengue disease, Congenital dermal sinus, Congenital diaphragmatic anomaly, Congenital diaphragmatic eventration, Congenital diaphragmatic hernia, Congenital disorder of glycosylation, Congenital dyserythropoietic anaemia, Congenital dysfibrinogenaemia, Congenital dyskeratosis, Congenital ectodermal dysplasia, Congenital ectopic bladder, Congenital ectopic pancreas, Congenital ectopic spleen, Congenital elevation of scapula, Congenital emphysema, Congenital endocrine anomaly, Congenital epiblepharon, Congenital epiglottal anomaly, Congenital eye disorder, Congenital eye naevus, Congenital eyelid malformation, Congenital facial diplegia, Congenital facial nerve hypoplasia, Congenital fallopian tube anomaly, Congenital female genital tract fistula, Congenital female reproductive tract disorder, Congenital fibrosarcoma, Congenital flaccid paralysis, Congenital flat feet, Congenital floppy infant, Congenital foot malformation, Congenital gastric anomaly, Congenital gastrointestinal vessel anomaly, Congenital generalised lipodystrophy, Congenital genital malformation, Congenital genital malformation female, Congenital genital malformation male, Congenital genitourinary abnormality, Congenital great vessel anomaly, Congenital growth hormone deficiency, Congenital haematological disorder, Congenital hair disorder, Congenital hand malformation, Congenital hearing disorder, Congenital heart valve disorder, Congenital heart valve incompetence, Congenital hemiparesis, Congenital hepatic fibrosis, Congenital hepatitis B infection, Congenital hepatitis C infection, Congenital hepatobiliary anomaly, Congenital hepatomegaly, Congenital herpes simplex infection, Congenital hiatus hernia, Congenital high airway obstruction syndrome, Congenital hydrocele renalis, Congenital hydrocephalus, Congenital hydronephrosis, Congenital hypercoagulation, Congenital hyperextension of knee, Congenital hyperextension of spine, Congenital hyperinsulinaemic hypoglycaemia, Congenital hyperthyroidism, Congenital hypertrichosis, Congenital hypogammaglobulinaemia, Congenital hypogonadotropic hypogonadism, Congenital hypoparathyroidism, Congenital hypoplasia of depressor angularis oris muscle, Congenital hypothyroidism, Congenital hypotransferrinaemia, Congenital infection, Congenital inguinal hernia, Congenital intestinal malformation, Congenital intestinal obstruction, Congenital intrahepatic arterioportal fistula, Congenital intrinsic factor deficiency, Congenital iris anomaly, Congenital jaw malformation, Congenital joint malformation, Congenital knee deformity, Congenital knee dislocation, Congenital kyphoscoliosis, Congenital labia pudendi adhesions, Congenital lacrimal gland anomaly, Congenital lacrimal passage anomaly, Congenital lactase deficiency, Congenital large intestinal atresia, Congenital laryngeal malformation, Congenital laryngeal stridor, Congenital lenticonus, Congenital leptin deficiency, Congenital limb hyperextension, Congenital lip fistula, Congenital lip pits, Congenital lymphatic dysplasia, Congenital lymphoedema, Congenital malaria, Congenital malignant neoplasm,

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Safety Topic	Preferred Term
	Congenital megacolon, Congenital megaureter, Congenital melanocytic naevus, Congenital melanosis, Congenital methaemoglobinaemia, Congenital midline defect, Congenital mitochondrial cytopathy, Congenital mitral valve incompetence, Congenital mitral valve stenosis, Congenital monorchidism, Congenital multiplex arthrogryposis, Congenital muscle absence, Congenital musculoskeletal disorder, Congenital musculoskeletal disorder of head and neck, Congenital musculoskeletal disorder of limbs, Congenital musculoskeletal disorder of skull, Congenital musculoskeletal disorder of spine, Congenital musculoskeletal disorder of trunk, Congenital myasthenic syndrome, Congenital myopathy, Congenital myopia, Congenital naevus, Congenital nail disorder, Congenital nasal septum deviation, Congenital neoplasm, Congenital nephrogenic diabetes insipidus, Congenital nephrotic syndrome, Congenital neurological degeneration, Congenital neurological disorder, Congenital neuropathy, Congenital night blindness, Congenital nipple anomaly, Congenital nipple inversion, Congenital nose malformation, Congenital nystagmus, Congenital oculomotor apraxia, Congenital oesophageal anomaly, Congenital oesophageal stenosis, Congenital oesophageal web, Congenital optic nerve anomaly, Congenital oral malformation, Congenital osteodystrophy, Congenital ovarian anomaly, Congenital oxalosis, Congenital pancreatic anomaly, Congenital parvovirus B19 infection, Congenital perforated nasal septum, Congenital pharyngeal anomaly, Congenital pigmentation disorder, Congenital pneumonia, Congenital poikiloderma, Congenital pseudarthrosis, Congenital pulmonary airway malformation, Congenital pulmonary artery anomaly, Congenital pulmonary hypertension, Congenital pulmonary valve atresia, Congenital pulmonary valve disorder, Congenital pyelocaliectasis, Congenital renal cyst, Congenital renal disorder, Congenital retinoblastoma, Congenital rubella infection, Congenital rubella syndrome, Congenital salivary gland anomaly, Congenital scleral disorder, Congenital scoliosis, Congenital scrotal hypertrophy, Congenital skin dimples, Congenital skin disorder, Congenital small intestinal atresia, Congenital spinal cord anomaly, Congenital spinal fusion, Congenital spinal stenosis, Congenital spondylolisthesis, Congenital spondylolysis, Congenital subglottic stenosis, Congenital supraventricular tachycardia, Congenital syphilis, Congenital syphilitic encephalitis, Congenital syphilitic meningitis, Congenital syphilitic osteochondritis, Congenital teratoma, Congenital thrombocyte disorder, Congenital thrombocytopenia, Congenital thymus absence, Congenital thyroid disorder, Congenital tongue anomaly, Congenital torticollis, Congenital toxoplasmosis, Congenital tracheomalacia, Congenital trichomegaly, Congenital tricuspid valve atresia, Congenital tricuspid valve incompetence, Congenital tricuspid valve stenosis, Congenital trigeminal anaesthesia, Congenital tuberculosis, Congenital umbilical hernia, Congenital umbilico-enteric fistula, Congenital ureteric anomaly, Congenital ureterocele, Congenital ureteropelvic junction obstruction, Congenital ureterovesical junction anomaly, Congenital urethral anomaly, Congenital urinary tract obstruction, Congenital uterine anomaly, Congenital vaccinia virus infection, Congenital vaginal cyst, Congenital varicella infection, Congenital varicocele, Congenital vas deferens absence, Congenital vena cava stenosis, Congenital vesicoureteric reflux, Congenital viral hepatitis, Congenital viral infection, Congenital visual acuity reduced, Congenital vitreous anomaly, Congenital vocal cord paralysis, Congenital white blood cell disorder, Conjoined twins, Conjunctivitis gonococcal neonatal, Connective tissue dysplasia, Constipation neonatal, Constricted ear deformity, Cor biloculare, Cor triatriatum, Cordocentesis, Corneal dystrophy, Corneal opacity congenital, Cornelia de Lange syndrome, Corrected transposition of great vessels, Cortical dysplasia, Costello syndrome, Cowden's disease, Coxsackie viral disease of the newborn, Cranial nerve injury secondary to birth trauma, Cranial sutures widening, Cranioectodermal dysplasia, Craniofacial deformity, Craniofacial dysostosis, Craniolacunia, Craniorachischisis, Craniosynostosis, Craniotabes, Creatine deficiency syndrome, Cri du Chat syndrome, Crigler-Najjar syndrome, Cryopyrin associated periodic syndrome, Cryptophthalmos, Cryptorchism, Cryptotia, Currarino syndrome, Cutaneovisceral angiomatosis with thrombocytopenia, Cyanosis neonatal, Cyclopia, Cystathionine beta-synthase deficiency, Cystic angiomatosis, Cystic eyeball, congenital, Cystic fibrosis, Cystic fibrosis carrier, Cystic fibrosis gastrointestinal disease, Cystic fibrosis hepatic disease, Cystic fibrosis lung, Cystic fibrosis pancreatic, Cystic fibrosis related diabetes, Cystinosis, Cystinuria, Cytogenetic abnormality, DDX3X syndrome, DNA mismatch repair protein gene mutation, DNMT3A gene mutation, DOOR syndrome, Dacryocystocoele, Dacryostenosis congenital, Dandy-Walker syndrome, De Barsy syndrome, De la Chapelle syndrome, Deaf mutism, Deafness congenital, Death neonatal, Decidual cast, Deficiency of the interleukin-1 receptor antagonist, Deficiency of the interleukin-36 receptor antagonist, Delayed closure of cranial sutures, Delayed delivery, Delayed foetal renal development, Delayed fontanelle closure, Delayed passage of meconium, Delayed umbilical cord

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	clamping, Delivery, Delivery outside health facility, Delta-beta thalassaemia, Dent's disease, Dentatorubral-pallidoluysian atrophy, Dentofacial anomaly, Denys-Drash syndrome, Dermatofibrosis lenticularis disseminata, Dermatoglyphic anomaly, Dermoid cyst, Desmin myopathy, Developmental glaucoma, Developmental hip dysplasia, Dextrocardia, DiGeorge's syndrome, Diabetes complicating pregnancy, Diabetic foetopathy, Diamine oxidase deficiency, Diaphragmatic aplasia, Diarrhoea infectious neonatal, Diastematomyelia, Diastrophic dysplasia, Diethylstilboestrol syndrome, Dihydropyrimidine dehydrogenase deficiency, Dilatation intrahepatic duct congenital, Discordant twin, Disorder of sex development, Disseminated intravascular coagulation in newborn, Disseminated neonatal herpes simplex, Disseminated superficial actinic porokeratosis, Distichiasis, Disturbance of thermoregulation of newborn, Diverticulitis Meckel's, Diverticulum of pharynx, congenital, Dolichocephaly, Dolichocolon, Donohue syndrome, Dopa-responsive dystonia, Double cortex syndrome, Double heterozygous sickling disorders, Double inlet left ventricle, Double outlet left ventricle, Double outlet right ventricle, Double ureter, Dowling-Degos disease, Drug administered to foetus, Drug dependence, antepartum, Drug dependence, postpartum, Drug exposure before pregnancy, Drug resistance mutation, Drug use disorder, antepartum, Drug use disorder, postpartum, Drug withdrawal syndrome neonatal, Dry lung syndrome, Duane's syndrome, Dubin-Johnson syndrome, Dubowitz syndrome, Duchenne muscular dystrophy, Duchenne muscular dystrophy gene carrier, Ductus arteriosus premature closure, Ductus arteriosus stenosis foetal, Ductus venosus agenesis, Duodenal atresia, Duplex appendix, Duplication of inferior vena cava, Dyke-Davidoff-Masson syndrome, Dyschondrosteosis, Dyschromatosis, Dysgnathia, Dyskinesia neonatal, Dysmorphism, Dysmyelination, Dysplastic naevus syndrome, EGFR gene mutation, EGFR gene overexpression, EZH2 gene mutation, Eagle Barrett syndrome, Ear malformation, Early infantile epileptic encephalopathy with burst-suppression, Early onset familial Alzheimer's disease, Early onset primary dystonia, Ebstein's anomaly, Eclampsia, Ectonucleotide pyrophosphatase/phosphodiesterase 1 deficiency, Ectopia cordis, Ectopic kidney, Ectopic ovary, Ectopic posterior pituitary gland, Ectopic pregnancy, Ectopic pregnancy termination, Ectopic pregnancy under hormonal contraception, Ectopic pregnancy with contraceptive device, Ectopic thyroid, Ectopic ureter, Ectrodactyly, Eczema infantile, Ehlers-Danlos syndrome, Elbow synostosis, Elderly primigravida, Elliptocytosis hereditary, Ellis-van Creveld syndrome, Emanuel syndrome, Emery-Dreifuss muscular dystrophy, Enameloma, Encephalocele, Encephalocutaneous angiomatosis, Encephalopathy neonatal, Endocardial cushion defect repair, Endocardial fibroelastosis, Endometritis bacterial, Endothelial protein C receptor polymorphism, Enlarged foetal cisterna magna, Enteric duplication, Entropion congenital, Epidermal naevus, Epidermal naevus syndrome, Epidermolysis, Epidermolysis bullosa, Epilepsy congenital, Epilepsy of infancy with migrating focal seizures, Epilepsy with myoclonic-atonic seizures, Epileptic encephalopathy, Epispadias, Erythema toxicum neonatorum, Erythroblastosis foetalis, Erythrokeratodermia variabilis, Essential fructosuria, Evacuation of retained products of conception, Excessive maternal gestational weight gain, Exomphalos, Exophthalmos congenital, Exposure during pregnancy, Exposure via father, External auditory canal atresia, External cephalic version, Extraocular retinoblastoma, Extrarenal pelvis, Eye anterior chamber congenital anomaly, Eyelid ptosis congenital, FGFR3 gene mutation, FLT3 gene mutation, Fabry's disease, Face presentation, Facial nerve injury due to birth trauma, Faciodigitogenital dysplasia, Facioscapulohumeral muscular dystrophy, Factor I deficiency, Factor II deficiency, Factor II mutation, Factor III deficiency, Factor IX deficiency, Factor V Leiden mutation, Factor V deficiency, Factor VII deficiency, Factor VIII deficiency, Factor X deficiency, Factor XI deficiency, Factor XII deficiency, Factor XIII deficiency, Failed forceps delivery, Failed induction of labour, Failed trial of labour, Failure to thrive, Fallot's pentalogy, Fallot's tetralogy, Fallot's trilogy, False labour, False negative pregnancy test, Familial acromegaly, Familial amyloidosis, Familial amyotrophic lateral sclerosis, Familial atrial fibrillation, Familial chondrocalcinosis, Familial cold autoinflammatory syndrome, Familial dilated cardiomyopathy, Familial gigantiform cementoma, Familial glucocorticoid deficiency, Familial haemophagocytic lymphohistiocytosis, Familial hemiplegic migraine, Familial high density lipoprotein deficiency, Familial hypertriglyceridaemia, Familial hypocalciuric hypercalcaemia, Familial infantile bilateral striatal necrosis, Familial isolated hyperparathyroidism, Familial mediterranean fever, Familial medullary thyroid cancer, Familial multiple lipomatosis, Familial partial lipodystrophy, Familial periodic paralysis, Familial polycythaemia, Familial renal glycosuria, Familial scaphocephaly syndrome, Familial tremor, Fanconi syndrome, Fatal familial insomnia, Fatty acid oxidation disorder, Feeding intolerance, Femoral anteversion, Femoral facial syndrome, Femoral

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Safety Topic	Preferred Term
	retroversion, Femur-fibula-ulna complex, Fever neonatal, Fibrodysplasia ossificans progressiva, Fibromatosis colli of infancy, Fibrous dysplasia of bone, Fibrous dysplasia of jaw, Fibula agenesis, Filippi syndrome, Finnegan score increased, First trimester pregnancy, Fissure of tongue, congenital, Fixed bowel loop, Floating-Harbor syndrome, Floppy infant, Foetal acidosis, Foetal alcohol spectrum disorder, Foetal alcohol syndrome, Foetal anaemia, Foetal anticonvulsant syndrome, Foetal arm prolapse, Foetal arrhythmia, Foetal biophysical profile score abnormal, Foetal biophysical profile score equivocal, Foetal brain scan abnormal, Foetal cardiac arrest, Foetal cardiac disorder, Foetal cardiac function test abnormal, Foetal cerebrovascular disorder, Foetal chromosome abnormality, Foetal compartment fluid collection, Foetal cystic hygroma, Foetal damage, Foetal death, Foetal disorder, Foetal distress syndrome, Foetal dystocia, Foetal exposure during delivery, Foetal exposure during pregnancy, Foetal exposure timing unspecified, Foetal gastrointestinal tract imaging abnormal, Foetal growth abnormality, Foetal growth restriction, Foetal heart rate abnormal, Foetal heart rate acceleration abnormality, Foetal heart rate deceleration abnormality, Foetal heart rate decreased, Foetal heart rate disorder, Foetal heart rate increased, Foetal heart rate indeterminate, Foetal heart rate normal, Foetal hypokinesia, Foetal macrosomia, Foetal malformation, Foetal malnutrition, Foetal malposition, Foetal malpresentation, Foetal megacystis, Foetal methotrexate syndrome, Foetal monitoring abnormal, Foetal movement disorder, Foetal musculoskeletal imaging abnormal, Foetal non-stress test abnormal, Foetal posterior cerebral artery, Foetal renal imaging abnormal, Foetal renal impairment, Foetal retinoid syndrome, Foetal surgery, Foetal tachyarrhythmia, Foetal therapeutic procedure, Foetal tobacco syndrome, Foetal vascular malperfusion, Foetal warfarin syndrome, Foetal-maternal haemorrhage, Foeticide, Fontanelle bulging, Fontanelle depressed, Foramen magnum stenosis, Forceps delivery, Fountain syndrome, Fracture of clavicle due to birth trauma, Fragile X carrier, Fragile X syndrome, Fraser syndrome, Frasier syndrome, Freeman-Sheldon syndrome, Frenulum breve, Friedreich's ataxia, Frontonasal dysplasia, Fructose-1,6-bisphosphatase deficiency, Fryns syndrome, Fumarase deficiency, Funisitis, GATA2 deficiency, GM2 gangliosidosis, GNE myopathy, GRACILE syndrome, Galactosaemia, Galactosialidosis, Gallbladder agenesis, Gallbladder anomaly congenital, Galloway Mowat syndrome, Gangrene neonatal, Gap junction protein beta 2 gene mutation, Gasping syndrome, Gastrointestinal arteriovenous malformation, Gastrointestinal disorder congenital, Gastrointestinal malformation, Gastrooesophageal reflux in neonate, Gastroschisis, Gatad2b associated neurodevelopmental disorder, Gaucher's disease, Gaucher's disease type I, Gaucher's disease type II, Gaucher's disease type III, Gene mutation, Generalised resistance to thyroid hormone, Genetic polymorphism, Geniospasm, Genital scarring, Genitalia external ambiguous, Gestational age test abnormal, Gestational alloimmune liver disease, Gestational diabetes, Gestational hypertension, Gestational oedema, Gestational trophoblastic detachment, Gilbert's syndrome, Gitelman's syndrome, Glanzmann's disease, Glucose tolerance impaired in pregnancy, Glucose transporter type 1 deficiency syndrome, Glucose-6-phosphate dehydrogenase deficiency, Glucose-galactose malabsorption, Glutaric acidaemia type I, Glutathione synthetase deficiency, Glycogen storage disease type I, Glycogen storage disease type II, Glycogen storage disease type III, Glycogen storage disease type IV, Glycogen storage disease type IX, Glycogen storage disease type V, Glycogen storage disease type VI, Glycogen storage disease type VII, Glycogen storage disease type VIII, Glycogen storage disorder, Glycoprotein metabolism disorder, Glycosuria during pregnancy, Gnathoschisis, Goitre congenital, Gollop-Wolfgang complex, Gonadal dysgenesis, Gorham's disease, Granulocytopenia neonatal, Greig's syndrome, Grey matter heterotopia, Grey syndrome neonatal, Griscelli syndrome, Group B streptococcus neonatal sepsis, Growth failure, H-ras gene mutation, H63D mutation, HELLP syndrome, HER2 gene amplification, HER2 protein overexpression, HERG gene mutation, Haber's syndrome, Habitual abortion, Haemangioma congenital, Haemangioma of retina, Haemochromatosis carrier, Haemochromatosis trait, Haemoglobin C disease, Haemoglobin C trait, Haemoglobin D disease, Haemoglobin D trait, Haemoglobin E disease, Haemoglobin E trait, Haemoglobin E-thalassaemia disease, Haemoglobin Lepore trait, Haemoglobinopathy, Haemolysis neonatal, Haemophilia, Haemophilia A with anti factor VIII, Haemophilia A without inhibitors, Haemophilia B with anti factor IX, Haemophilia B without inhibitors, Haemophilia carrier, Haemopyrrollactamuria, Haemorrhage foetal, Haemorrhage in pregnancy, Haemorrhage neonatal, Haemorrhagic arteriovenous malformation, Haemorrhagic disease of newborn, Hamartoma, Hamartoma vascular, Hand-foot-genital syndrome, Haploinsufficiency of A20, Harlequin foetus, Hartnup disease, Head circumference abnormal, Heart block congenital, Heart disease congenital, Hemihypertrophy, Hemivertebra, Heparin cofactor II

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Safety Topic	Preferred Term
	deficiency, Hepatic arteriovenous malformation, Hepatic hamartoma, Hepatitis neonatal, Hepato-lenticular degeneration, Hepatocellular damage neonatal, Hepatosplenomegaly neonatal, Hereditary ATTR amyloid cardiomyopathy, Hereditary alpha tryptasaemia, Hereditary angioedema, Hereditary angioedema with C1 esterase inhibitor deficiency, Hereditary angioedema with normal C1 esterase inhibitor, Hereditary areflexic dystasia, Hereditary ataxia, Hereditary cerebral degeneration, Hereditary choroidal dystrophy, Hereditary disorder, Hereditary fructose intolerance, Hereditary gingival fibromatosis, Hereditary haemochromatosis, Hereditary haemolytic anaemia, Hereditary haemorrhagic telangiectasia, Hereditary hypophosphataemic rickets, Hereditary leiomyomatosis renal cell carcinoma, Hereditary microcytic anaemia, Hereditary motor and sensory neuropathy, Hereditary motor neurone disease, Hereditary multiple osteochondromas, Hereditary neuropathic amyloidosis, Hereditary neuropathy with liability to pressure palsies, Hereditary non-polyposis colorectal cancer syndrome, Hereditary optic atrophy, Hereditary palmoplantar keratoderma, Hereditary pancreatitis, Hereditary papillary renal carcinoma, Hereditary persistence of foetal haemoglobin, Hereditary renal microhaematuria, Hereditary retinal dystrophy, Hereditary sideroblastic anaemia, Hereditary spastic paraplegia, Hereditary spherocytosis, Hereditary stomatocytosis, Hereditary xerocytosis, Heritable pulmonary arterial hypertension, Hermansky-Pudlak syndrome, Hermaphroditism, Hernia congenital, Herpes gestationis, Herpes simplex virus conjunctivitis neonatal, Heterochromia iridis, Heterotaxia, Heterotopic pregnancy, Hexokinase deficiency anaemia, High arched palate, High foetal head, High risk infant, High risk pregnancy, High-pitched crying, Histiocytosis-lymphadenopathy plus syndrome, Hollow visceral myopathy, Holoprosencephaly, Holt-Oram syndrome, Homocystinaemia, Homocystinuria, Hooded prepuce, Human chorionic gonadotropin increased, Human chorionic gonadotropin positive, Huntington's disease, Hydranencephaly, Hydrocele, Hydrops foetalis, Hydroxyprolinaemia, Hygroma colli, Hyper IgD syndrome, Hyper IgE syndrome, Hyper IgM syndrome, Hyperbilirubinaemia neonatal, Hyperemesis gravidarum, Hyperexplexia, Hyperglycinaemia, Hyperkinesia neonatal, Hyperlysinaemia, Hypermethioninaemia, Hypermethioniuria, Hypermobility syndrome, Hypermutation, Hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome, Hyperphenylalaninaemia, Hyperpipecolic acidaemia, Hyperprolinaemia, Hyperreactio luteinalis, Hypersplenism congenital, Hypertelorism, Hypertension neonatal, Hypertonia neonatal, Hypertrophic cardiomyopathy, Hypocalvaria, Hypochondroplasia, Hypoglycaemia neonatal, Hypokinesia neonatal, Hypomelanosis of Ito, Hypophosphatasia, Hypopituitarism foetal, Hypoplastic left heart syndrome, Hypoplastic nasal cartilage, Hypoplastic right heart syndrome, Hypospadias, Hypotelorism of orbit, Hypothalamic hamartoma, Hypothermia neonatal, Hypotonia neonatal, Hypotonia-cystinuria syndrome, Hypoventilation neonatal, Hypoxanthine-guanine phosphoribosyl transferase deficiency, Hypoxic ischaemic encephalopathy neonatal, IPEX syndrome, Ichthyosis, Immature larynx, Immature respiratory system, Imminent abortion, Immunodeficiency congenital, Imperforate hymen, Imperforate oesophagus, Impetigo herpetiformis, Inborn error of amino acid metabolism, Inborn error of bilirubin metabolism, Inborn error of lipid metabolism, Inborn error of metabolism, Inborn error of steroid synthesis, Inclusion conjunctivitis neonatal, Incoordinate uterine action, Increased foetal movements, Incubator therapy, Induced abortion failed, Induced abortion haemorrhage, Induced abortion infection, Induced labour, Induction of cervix ripening, Infant dyschezia, Infant irritability, Infant sedation, Infantile acropustulosis, Infantile apnoea, Infantile back arching, Infantile colic, Infantile cortical hyperostosis, Infantile diarrhoea, Infantile fibromatosis, Infantile genetic agranulocytosis, Infantile haemangioma, Infantile neuroaxonal dystrophy, Infantile postural asymmetry, Infantile scurvy, Infantile septic granulomatosis, Infantile spasms, Infantile spitting up, Infantile vomiting, Inferior vena cava syndrome, Inherited cardiac conduction disorder, Inherited otosclerosis, Iniencephaly, Injury to brachial plexus due to birth trauma, Injury to spinal cord secondary to birth trauma, Interferon gamma receptor deficiency, Interleukin 28B polymorphism, Interruption of aortic arch, Intestinal atresia, Intestinal malrotation, Intestinal neuronal dysplasia, Intestinal transposition, Intoxication by breast feeding, Intracranial arterial fenestration, Intracranial haemorrhage neonatal, Intracranial lipoma, Intrapartum haemorrhage, Intrauterine infection, Intraventricular haemorrhage neonatal, Iris coloboma, Iris hamartoma, Isocitrate dehydrogenase gene mutation, Isodicentric chromosome 15 syndrome, Isoimmune haemolytic disease, Isovaleric acidaemia, JAG1 gene mutation, Jacobsen syndrome, Jansen's metaphyseal chondrodysplasia, Janus kinase 2 mutation, Jaundice neonatal, Johanson-Blizzard syndrome, Joubert syndrome, Junctional ectopic tachycardia, Juvenile Paget's disease, Juvenile polyposis syndrome, K-ras gene mutation, KBG syndrome, KMT2A gene mutation,

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Safety Topic	Preferred Term
	Kabuki make-up syndrome, Kaufman-McKusick syndrome, Kearns-Sayre syndrome, Kenny-Caffey syndrome, Keratitis-ichthyosis-deafness syndrome, Keratolysis exfoliativa congenital, Keratosis follicular, Kernicterus, Kidney duplex, Kidney malformation, Kidney malrotation, Kimmerle's anomaly, Kinematic imbalances due to suboccipital strain, Kleefstra syndrome, Kleihauer-Betke test positive, Klinefelter's syndrome, Klippel-Feil syndrome, Klippel-Trenaunay syndrome, Kniest dysplasia, Kommerell's diverticulum, Kosaki overgrowth syndrome, Krabbe's disease, Kyphosis congenital, LDLR mutation, Laband syndrome, Labour augmentation, Labour complication, Labour induction, Labour pain, Labour stimulation, Labrune syndrome, Lacrimal punctum agenesis, Lacrimo-auriculo-dento-digital syndrome, Laevocardia, Lafora's myoclonic epilepsy, Lamin A/C gene mutation, Langer-Giedion syndrome, Large for dates baby, Laron syndrome, Larsen syndrome, Laryngeal cleft, Laryngeal web, Laryngo-onycho-cutaneous syndrome, Laryngocele, Laryngomalacia, Late metabolic acidosis of newborn, Laurence-Moon-Bardet-Biedl syndrome, Leber's congenital amaurosis, Lecithin-cholesterol acyltransferase deficiency, Left ventricle outflow tract obstruction, Left ventricular false tendon, Left-to-right cardiac shunt, Lens abnormality, congenital, Lenticulostriatal vasculopathy, Leptin receptor deficiency, Leukocyte adhesion deficiency type I, Leukodystrophy, Leukopenia neonatal, Li-Fraumeni syndrome, Lichen spinulosus, Liddle's syndrome, Limb hypoplasia congenital, Limb reduction defect, Lipid proteinosis, Lipidosis, Lipodermoid tumour, Lipomeningocele, Lissencephaly, Lithopedion, Live birth, Lochial infection, Lochiostasis, Locked twins, Loeys-Dietz syndrome, Long QT syndrome congenital, Long-chain acyl-coenzyme A dehydrogenase deficiency, Loose anagen syndrome, Low birth weight baby, Low set ears, Lown-Ganong-Levine syndrome, Lowry-Wood syndrome, Lumbarisation, Lymphangiectasia intestinal congenital, Lymphatic malformation, Lymphocytic hypophysitis, Lymphocytopenia neonatal, Lysinuric protein intolerance, Lysosomal acid lipase deficiency, Lysosomal storage disorder, MELAS syndrome, MLASA syndrome, MPL gene mutation, MYH9-related disease, Macrocephaly, Macrocheilia, Macrocornea, Macrodactyly, Macrogenia, Macroglossia, Macrognathia, Macrophthalmos, Macrostomia, Macrotia, Macular dystrophy congenital, Macular hypoplasia, Mainzer-Saldino syndrome, Majeed's syndrome, Malformation biliary, Malformation venous, Malignant hydatidiform mole, Malignant neoplasm of placenta, Mandibulofacial dysostosis, Mannose-binding lectin deficiency, Maple syrup disease, Marcus Gunn syndrome, Marfan's syndrome, Marfanoid habitus, Mastitis postpartum, Maternal alcohol use, Maternal body mass index decreased, Maternal body mass index increased, Maternal cancer in pregnancy, Maternal condition affecting foetus, Maternal death, Maternal death affecting foetus, Maternal disease complicating pregnancy, Maternal distress during labour, Maternal drugs affecting foetus, Maternal exposure before pregnancy, Maternal exposure during delivery, Maternal exposure during pregnancy, Maternal exposure timing unspecified, Maternal exposure via partner during pregnancy, Maternal hypertension affecting foetus, Maternal pre-pregnancy obesity, Maternal pre-pregnancy underweight, Maternal therapy to enhance foetal lung maturity, Maternal-foetal therapy, Maternally inherited diabetes and deafness, Maxillonasal dysplasia, Mayer-Rokitansky-Kuster-Hauser syndrome, Mazabraud's syndrome, McLeod neuroacanthocytosis syndrome, Meconium abnormal, Meconium aspiration syndrome, Meconium cyst, Meconium ileus, Meconium in amniotic fluid, Meconium increased, Meconium peritonitis, Meconium plug syndrome, Meconium stain, Medically induced preterm birth, Medium-chain acyl-coenzyme A dehydrogenase deficiency, Megalencephaly, Meier-Gorlin syndrome, Melaena neonatal, Melanocortin 4 receptor deficiency, Melkersson-Rosenthal syndrome, Membranous lipodystrophy, Meningitis neonatal, Meningocele, Meningoencephalitis herpes simplex neonatal, Meningomyelocele, Menkes' syndrome, Mesoblastic nephroma, Mesonephric duct cyst, Metabolic myopathy, Metachromatic leukodystrophy, Metaphyseal dysplasia, Metastases to placenta, Metatarsus primus varus, Metatropic dysplasia, Methylenetetrahydrofolate reductase deficiency, Methylenetetrahydrofolate reductase gene mutation, Methylenetetrahydrofolate reductase polymorphism, Methylmalonic acidaemia, Mevalonate kinase deficiency, Mevalonic aciduria, Microcephaly, Microcheilia, Microcolon, Microcornea, Microencephaly, Microgenia, Microglossia, Micrognathia, Microorchidism, Micropenis, Microphthalmos, Microstomia, Microtia, Microvillous inclusion disease, Midline head position, Mirror syndrome, Mismatch repair cancer syndrome, Missed labour, Mitochondrial DNA deletion, Mitochondrial DNA depletion, Mitochondrial DNA duplication, Mitochondrial DNA mutation, Mitochondrial cardiomyopathy, Mitochondrial encephalomyopathy, Mitochondrial enzyme deficiency, Mitochondrial hepatopathy, Mitochondrial myopathy, Mitochondrial neurogastrointestinal encephalopathy, Mitral valve atresia, Mitral valve dysplasia, Mittendorf dot, Mobile caecum syndrome, Molar abortion, Molybdenum

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Safety Topic	Preferred Term
	cofactor deficiency, Monolid eyes, Monopodia, Morgagni-Stewart-Morel syndrome, Morning glory syndrome, Morning sickness, Morton's syndrome, Mosaicism, Mount-Reback syndrome, Muckle-Wells syndrome, Mucolipidosis, Mucolipidosis type I, Mucolipidosis type II, Mucolipidosis type III, Mucolipidosis type IV, Mucopolysaccharidosis, Mucopolysaccharidosis I, Mucopolysaccharidosis II, Mucopolysaccharidosis III, Mucopolysaccharidosis IV, Mucopolysaccharidosis IX, Mucopolysaccharidosis V, Mucopolysaccharidosis VI, Mucopolysaccharidosis VII, Muenke syndrome, Muir-Torre syndrome, Multigravida, Multiparous, Multiple carboxylase deficiency, Multiple cardiac defects, Multiple congenital abnormalities, Multiple cutaneous and uterine leiomyomatosis, Multiple endocrine neoplasia, Multiple endocrine neoplasia Type 1, Multiple endocrine neoplasia Type 2, Multiple endocrine neoplasia Type 2A, Multiple endocrine neoplasia Type 2B, Multiple epiphyseal dysplasia, Multiple lentigines syndrome, Multiple pregnancy, Muscle-eye-brain disease, Muscular dystrophy, Mutagenic effect, Mutchinick syndrome, MyBPC3 gene mutation, Myasthenia gravis neonatal, Mycoplasmal postabortal fever, Myeloperoxidase deficiency, Myocardial bridging, Myoclonic dystonia, Myoclonic epilepsy and ragged-red fibres, Myoclonus epilepsy and ataxia due to potassium channel mutation, Myofibrillar myopathy, Myotonia congenita, Myotonic dystrophy, N-acetylglutamate synthase deficiency, N-ras gene mutation, NAT1 polymorphism, NAT2 polymorphism, NPM1 gene mutation, NR5A1 gene mutation, NTRK gene amplification, NTRK gene fusion overexpression, NUDT15 polymorphism, NUT gene mutation, Naevus anaemicus, Naevus flammeus, Naevus spider congenital, Nager syndrome, Nail aplasia, Nail dysplasia, Nail-patella syndrome, Nakajo-Nishimura syndrome, Nasopalatine duct cyst, Nasopharyngeal atresia, Necrotising enterocolitis neonatal, Neonatal Crohn's disease, Neonatal alloimmune thrombocytopenia, Neonatal alveolar aeration excessive, Neonatal anoxia, Neonatal anuria, Neonatal asphyxia, Neonatal aspiration, Neonatal bacteraemia, Neonatal bacterial pneumonia, Neonatal behavioural syndrome, Neonatal bradyarrhythmia, Neonatal candida infection, Neonatal cardiac failure, Neonatal cholestasis, Neonatal complications of substance abuse, Neonatal deafness, Neonatal deformity, Neonatal diabetes mellitus, Neonatal disorder, Neonatal dyspnoea, Neonatal epileptic seizure, Neonatal exchange blood transfusion, Neonatal gastrointestinal disorder, Neonatal gastrointestinal haemorrhage, Neonatal haemochromatosis, Neonatal hepatomegaly, Neonatal hyperglycaemia, Neonatal hypoacusis, Neonatal hypocalcaemia, Neonatal hyponatraemia, Neonatal hypoparathyroidism, Neonatal hypotension, Neonatal hypoxia, Neonatal infection, Neonatal infective mastitis, Neonatal intestinal dilatation, Neonatal intestinal obstruction, Neonatal intestinal perforation, Neonatal leukaemia, Neonatal lupus erythematosus, Neonatal mucocutaneous herpes simplex, Neonatal multi-organ failure, Neonatal neuroblastoma, Neonatal oversedation, Neonatal pneumonia, Neonatal pneumothorax, Neonatal pulmonary hypertension, Neonatal respiratory acidosis, Neonatal respiratory alkalosis, Neonatal respiratory arrest, Neonatal respiratory depression, Neonatal respiratory distress, Neonatal respiratory distress syndrome, Neonatal respiratory distress syndrome prophylaxis, Neonatal respiratory failure, Neonatal seizure, Neonatal sinus bradycardia, Neonatal sinus tachycardia, Neonatal tachyarrhythmia, Neonatal tachycardia, Neonatal tachypnoea, Neonatal testicular torsion, Neonatal tetany, Neonatal thyrotoxicosis, Neonatal toxicity, Neonatal warming therapy, Netherton's syndrome, Neural tube defect, Neuroacanthocytosis, Neuroblastoma, Neurodegeneration with brain iron accumulation disorder, Neuroendocrine cell hyperplasia of infancy, Neurofibromatosis, Neuronal ceroid lipofuscinosis, Neuronal migration disorder, Neuropathy, ataxia, retinitis pigmentosa syndrome, Neutropenia neonatal, Neutrophil Fc gamma RIIIb deficiency, Newborn head moulding, Newborn persistent pulmonary hypertension, Niemann-Pick disease, Nievergelt-Pearlman syndrome, Nijmegen breakage syndrome, Non-compaction cardiomyopathy, Nonreassuring foetal heart rate pattern, Noonan syndrome, Normal foetus, Normal labour, Normal newborn, Norrie's disease, Norwood procedure, Nulliparous, OHVIRA syndrome, Oblique presentation, Obstetric infection, Obstetric procedure complication, Obstetrical pulmonary embolism, Obstetrical tetanus, Obstructed labour, Ocular albinism, Oculo-digito-oesophageal-duodenal syndrome, Oculoauriculovertebral dysplasia, Oculocerebrocutaneous syndrome, Oculocerebrorenal syndrome, Oculodentodigital dysplasia, Oculopharyngeal dystrophy, Odontogenic cyst, Odontoid process hypoplasia, Odontoma, Oedema neonatal, Oesophageal atresia, Oesophageal cyst, Oestrogen receptor gene overexpression, Ogden syndrome, Olfacto genital dysplasia, Olfactory nerve agenesis, Oligohydramnios, Olmsted syndrome, Omenn syndrome, Omphalitis, Omphalorrhexis, Ophthalmia neonatorum, Opitz trigonocephaly syndrome, Opitz-G/BBB syndrome, Optic disc pit, Optic nerve hypoplasia, Oral-facial-digital syndrome

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Safety Topic	Preferred Term
	type II, Ornithine transcarbamoylase deficiency, Oroticaciduria congenital, Os trigonum, Osteochondrodysplasia, Osteogenesis imperfecta, Osteopathia striata, Osteopetrosis, Osteopoikilosis, Osteoporosis-pseudoglioma syndrome, Ota's naevus, Otocephaly, Otopalatodigital spectrum disorder, Otospondylomegaepiphyseal dysplasia, Ovarian agenesis, Ovarian hypoplasia, Ovarioleukodystrophy, Overfeeding of infant, Overgrowth syndrome, Oxycephaly, PACS1 neurodevelopmental disorder, PAPSS2 gene mutation, PCDH19 gene mutation, PCSK9 gene mutation, PHACES syndrome, PIK3CA related overgrowth spectrum, PIK3CA-activated mutation, PRPF8 gene mutation, PSTPIP1-associated myeloid-related proteinaemia inflammatory syndrome, PTEN gene mutation, PTPN11 gene mutation, PURA syndrome, Pachydermoperiostosis, Pachygyria, Pachyonychia congenita, Pallister W syndrome, Pallister-Hall syndrome, Pallister-Killian syndrome, Pancreas divisum, Papillon-Lefevre syndrome, Parachute mitral valve, Paraduodenal hernia, Paramyotonia congenita, Paranasal sinus aplasia, Paranasal sinus hypoplasia, Parenteral nutrition associated liver disease, Parity, Parkes-Weber syndrome, Paroxysmal extreme pain disorder, Patent ductus arteriosus, Patent ductus arteriosus repair, Paternal drugs affecting foetus, Paternal exposure before pregnancy, Paternal exposure during pregnancy, Paternal exposure timing unspecified, Pearson's syndrome, Pectus carinatum, Pectus excavatum, Pelizaeus-Merzbacher disease, Pelvic girdle pain, Pelvic haematoma obstetric, Pelvic kidney, Pendred syndrome, Penile torsion, Penoscrotal fusion, Penoscrotal transposition, Penta X syndrome, Perinatal HBV infection, Perinatal HIV infection, Perinatal brain damage, Perinatal stroke, Perineal haematoma, Perineal injury, Perineal repair breakdown, Perineal swelling, Periodontal congenital anomaly, Peripartum cardiomyopathy, Peripartum haemorrhage, Peripheral oedema neonatal, Periventricular haemorrhage neonatal, Periventricular leukomalacia, Perlman syndrome, Perry syndrome, Persistent Muellerian duct syndrome, Persistent cloaca, Persistent foetal circulation, Persistent left superior vena cava, Persistent pupillary membrane, Persistent urogenital sinus, Peutz-Jeghers syndrome, Pfeiffer syndrome, Phakomatosis, Phalangeal agenesis, Phalangeal hypoplasia, Phelan-McDermid syndrome, Phenylketonuria, Phimosis, Phytosterolaemia, Piebaldism, Pilonidal cyst congenital, Pituitary infarction, Pituitary stalk interruption syndrome, Placenta accreta, Placenta duplex, Placenta praevia, Placenta praevia haemorrhage, Placental calcification, Placental chorioangioma, Placental cyst, Placental disorder, Placental dysplasia, Placental hypertrophy, Placental infarction, Placental insufficiency, Placental lake, Placental necrosis, Placental neoplasm, Placental oedema, Placental polyp, Placental transfusion syndrome, Plagiocephaly, Planning to become pregnant, Plasminogen activator inhibitor polymorphism, Plasminogen activator inhibitor type 1 deficiency, Platelet glycoprotein gene mutation, Platelet storage pool deficiency, Platelet-derived growth factor receptor gene mutation, Platelet-derived growth factor receptor overexpression, Platonychia, Platybasia, Platyspondylia, Pleural malformation, Poirier-Bienvenu neurodevelopmental syndrome, Poland's syndrome, Polycystic liver disease, Polycythaemia neonatorum, Polydactyly, Polyhydramnios, Polymicrogyria, Polymorphic eruption of pregnancy, Polyorchidism, Poor feeding infant, Poor sucking reflex, Poor weight gain neonatal, Popliteal pterygium syndrome, Porencephaly, Porokeratosis, Porphyria, Porphyria acute, Porphyria non-acute, Porphyrin metabolism disorder, Porphyrinuria, Portal venous system anomaly, Post abortion complication, Post abortion haemorrhage, Post abortion infection, Postauricular fistula, Posterior segment of eye anomaly congenital, Posthaemorrhagic hydrocephalus, Postmature baby, Postnatal growth restriction, Postpartum anxiety, Postpartum disorder, Postpartum haemorrhage, Postpartum hypopituitarism, Postpartum neurosis, Postpartum sepsis, Postpartum state, Postpartum stress disorder, Postpartum thrombosis, Postpartum uterine subinvolution, Postpartum venous thrombosis, Postponement of preterm delivery, Potter's syndrome, Prader-Willi syndrome, Pre-eclampsia, Preauricular cyst, Precipitate labour, Preduodenal portal vein, Pregnancy, Pregnancy after post coital contraception, Pregnancy in habitual aborter, Pregnancy of partner, Pregnancy of unknown location, Pregnancy on contraceptive, Pregnancy on oral contraceptive, Pregnancy related infection, Pregnancy test positive, Pregnancy test urine positive, Pregnancy with advanced maternal age, Pregnancy with contraceptive device, Pregnancy with contraceptive patch, Pregnancy with implant contraceptive, Pregnancy with injectable contraceptive, Pregnancy with young maternal age, Premature baby, Premature baby death, Premature delivery, Premature labour, Premature rupture of membranes, Premature separation of placenta, Prenatal care, Prenatal screening test abnormal, Preterm premature rupture of membranes, Preternatural anus, Previous caesarean section, Primary bilateral macronodular adrenal hyperplasia, Primary cerebellar degeneration, Primary ciliary dyskinesia, Primary coenzyme Q10 deficiency, Primary familial brain

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Safety Topic	Preferred Term
	calcification, Primary familial hypomagnesaemia, Primary hypercholesterolaemia, Primary hyperoxaluria, Primary immunodeficiency syndrome, Primary insulin like growth factor-1 deficiency, Primigravida, Primiparous, Pro-opiomelanocortin deficiency, Progeria, Progesterone receptor gene overexpression, Progressive cerebellar degeneration, Progressive diaphyseal dysplasia, Progressive encephalopathy, hypsarrhythmia and optic atrophy syndrome, Progressive external ophthalmoplegia, Progressive familial intrahepatic cholestasis, Progressive myoclonic epilepsy, Prolonged labour, Prolonged pregnancy, Prolonged rupture of membranes, Prominent epicanthal folds, Prophylaxis against Rh isoimmunisation, Prophylaxis of abortion, Propionic acidaemia, Protein C deficiency, Protein S deficiency, Proteus syndrome, Protuberant ear, Proximal focal femoral deficiency, Prurigo of pregnancy, Pseudocholinesterase deficiency, Pseudohermaphroditism, Pseudohermaphroditism female, Pseudohermaphroditism male, Pseudohypoaldosteronism, Pseudohypoparathyroidism, Pseudotruncus arteriosus, Pseudoxanthoma elasticum, Pterygium colli, Puerperal infection, Puerperal pyrexia, Pulmonary air leakage, Pulmonary aplasia, Pulmonary arteriovenous fistula, Pulmonary artery atresia, Pulmonary artery stenosis congenital, Pulmonary dysmaturity syndrome, Pulmonary haemorrhage neonatal, Pulmonary hypoplasia, Pulmonary lymphangiectasia, Pulmonary malformation, Pulmonary oedema neonatal, Pulmonary sequestration, Pulmonary valve stenosis congenital, Purine nucleoside phosphorylase deficiency, Purpura neonatal, Pycnodysostosis, Pyloric stenosis, Pyloromyotomy, Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome, Pyriform aperture stenosis, Pyruvate carboxylase deficiency, Pyruvate dehydrogenase complex deficiency, Pyruvate kinase deficiency anaemia, RBM20 mutation, RET gene amplification, RET gene mutation, RET gene overexpression, ROS1 gene rearrangement, RPE65 gene mutation, RUNX1 gene mutation, Rabson-Mendenhall syndrome, Radial dysplasia, Radiation injury affecting foetus, Raine syndrome, Rapadilino syndrome, Rapid-onset dystonia-parkinsonism, Rash neonatal, Rathke's cleft cyst, Rectal atresia, Red blood cell enzymes abnormal, Refsum's disease, Renal aplasia, Renal arteriovenous malformation, Renal disorder in pregnancy, Renal dysplasia, Renal failure neonatal, Renal fusion anomaly, Renal hypoplasia, Renal impairment neonatal, Renal malposition, Renal vessel congenital anomaly, Repair of imperforate rectum, Reproductive tract hypoplasia, male, Reproductive tract procedural infection, Respiratory disorder neonatal, Respiratory tract haemorrhage neonatal, Respiratory tract malformation, Retained placenta operation, Retained placenta or membranes, Retained products of conception, Retinal anomaly congenital, Retinal arteriovenous malformation, Retinal coloboma, Retinitis pigmentosa, Retinopathy congenital, Retinopathy of prematurity, Retinoschisis congenital, Retroplacental haematoma, Rett syndrome, Reversible cerebral vasoconstriction syndrome, Rhesus haemolytic disease of newborn, Rhesus incompatibility, Rib hypoplasia, Rib synostosis, Riedel lobe, Right aortic arch, Right ventricle outflow tract obstruction, Right ventricular false tendon, Right-to-left cardiac shunt, Riley-Day syndrome, Ring chromosome, Rippling muscle disease, Risk of future pregnancy miscarriage, Roberts syndrome, Robinow syndrome, Rotor's syndrome, Rubella in pregnancy, Rubinstein-Taybi syndrome, Ruptured ectopic pregnancy, SADDAN syndrome, SATB2-associated syndrome, SF3B1 gene mutation, SRSF2 gene mutation, STAG2 gene mutation, STING-associated vasculopathy with onset in infancy, Sacral hypoplasia, Sacralisation, Saposin C deficiency, Sarcoglycanopathy, Sarcosinaemia, Scalp injury due to birth trauma, Scaphocephaly, Schimke immunoosseous dysplasia, Schinzel syndrome, Schinzel-Giedion syndrome, Schizencephaly, Schmid Fraccaro syndrome, Schwartz Jampel syndrome, Scimitar syndrome, Sclerocornea, Sclerotylosis, Sebaceous naevus, Second trimester pregnancy, Selective abortion, Seminal vesicle agenesis, Senior-Loken syndrome, Sensory neuropathy hereditary, Sepsis neonatal, Septate hymen, Septo-optic dysplasia, Septum pellucidum agenesis, Sertoli-cell-only syndrome, Severe myoclonic epilepsy of infancy, Severe primary insulin like growth factor-1 deficiency, Sex chromosome abnormality, Shawl scrotum, Shone complex, Short anagen syndrome, Short interpregnancy interval, Short stature homeobox gene mutation, Short-chain acyl-coenzyme A dehydrogenase deficiency, Shortened cervix, Shoulder dystocia, Shprintzen-Goldberg syndrome, Shwachman-Diamond syndrome, Sickle cell anaemia, Sickle cell disease, Sickle cell trait, Silent thyroiditis, Silver-Russell syndrome, Simpson-Golabi-Behmel syndrome, Single atrium, Single umbilical artery, Sinusoidal foetal heart rate pattern, Sirenomelia, Sjogren-Larsson syndrome, Skeletal dysplasia, Skin hypoplasia, Skin malformation, Small fontanelle, Small for dates baby, Small patella syndrome, Small size placenta, Smith-Lemli-Opitz syndrome, Smith-Magenis syndrome, Solitary median maxillary central incisor syndrome, Somnolence neonatal, Sotos' syndrome, Special senses congenital anomaly, Spherophakia,

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Safety Topic	Preferred Term
	Spina bifida, Spina bifida cystica, Spina bifida occulta, Spinal muscular atrophy, Spinal vessel congenital anomaly, Spleen malformation, Splenic hamartoma, Split hand nystagmus syndrome, Spondylocostal dysostosis, Spondyloepiphyseal dysplasia, Spontaneous rupture of membranes, Sporadic infantile bilateral striatal necrosis, Stahl's ear, Stargardt's disease, Steatocystoma multiplex, Stickler's syndrome, Sticky platelet syndrome, Stiff skin syndrome, Stillbirth, Strabismus congenital, Straddling tricuspid valve, Sturge-Weber syndrome, Subaponeurotic cerebrospinal fluid collection of infancy, Subarachnoid haemorrhage neonatal, Subchorionic haematoma, Subchorionic haemorrhage, Subdural haemorrhage neonatal, Subgaleal haematoma, Subgaleal haemorrhage, Suck-swallow breathing coordination disturbance, Sucrase-isomaltase deficiency, Sudden infant death syndrome, Superimposed pre-eclampsia, Supernumerary nipple, Supernumerary rib, Supernumerary teeth, Supernumerary vertebra, Swyer syndrome, Symphysiotomy, Syndactyly, Synostosis, Syringomyelia, Systemic artery to pulmonary artery fistula, Systemic right ventricle, Systemic-pulmonary artery shunt, TET2 gene mutation, TNFAIP3 mutation, TORCH infection, TP53 gene mutation, TRPV4 gene mutation, Tachycardia foetal, Talipes, Tangier disease, Taurodontism, Telangiectasia congenital, Teratogenicity, Term baby, Term birth, Testicular dysplasia, Testotoxicosis, Tetanus neonatorum, Tethered oral tissue, Tetrahydrobiopterin deficiency, Tetralogy of Fallot repair, Thalassaemia, Thalassaemia alpha, Thalassaemia beta, Thalassaemia minor, Thalassaemia sickle cell, Thalidomide embryopathy, Thanatophoric dysplasia, Thiopurine methyltransferase polymorphism, Third stage postpartum haemorrhage, Third trimester pregnancy, Threatened labour, Threatened uterine rupture, Thrombocytopenia neonatal, Thrombocytopenia-absent radius syndrome, Thrombophlebitis neonatal, Thymus enlargement, Thymus hypoplasia, Thyroglossal cyst, Thyroglossal fistula, Thyroid dysfunction in pregnancy, Thyroid hemiagenesis, Thyroid malformation, Tibial agenesis, Tibial torsion, Tilted disc syndrome, Timothy syndrome, Tocolysis, Tooth agenesis, Tooth discolouration congenital, Tooth hypoplasia, Tooth malformation hereditary, Tornwaldt cyst, Tourette's disorder, Tracheal atresia, Tracheal web, Tracheloplasty, Tracheo-oesophageal fistula, Tracheobronchomegaly, Transcobalamin deficiency, Transgenerational epigenetic inheritance, Transient hypogammaglobulinaemia of infancy, Transient neonatal hyperthyrotropinaemia, Transient neonatal pustular melanosis, Transient tachypnoea of the newborn, Transitional vertebrae, Transmembrane receptor tyrosine kinase overexpression, Transposition of the great vessels, Transverse presentation, Traumatic delivery, Tremor neonatal, Trichorhinophalangeal syndrome, Trifunctional protein deficiency, Trimethylaminuria, Triple A syndrome, Triploid syndrome, Trisomy 11, Trisomy 12, Trisomy 13, Trisomy 14, Trisomy 15, Trisomy 16, Trisomy 17, Trisomy 18, Trisomy 21, Trisomy 22, Trisomy 4p, Trisomy 8, Trisomy 9, Truncus arteriosus persistent, Truncus arteriosus repair, Tubal rupture, Tuberous sclerosis complex, Tumour necrosis factor receptor-associated periodic syndrome, Turner's syndrome, Twin pregnancy, Twin reversed arterial perfusion sequence malformation, Tympanomeningeal fissure, Type I hyperlipidaemia, Type II hyperlipidaemia, Type III hyperlipidaemia, Type IIa hyperlipidaemia, Type IIb hyperlipidaemia, Type IV hyperlipidaemia, Type V hyperlipidaemia, Tyrosinaemia, Tyrosine kinase mutation, U2AF1 gene mutation, UGT1A1 gene mutation, UGT1A1 gene polymorphism, Uhl's anomaly, Ulnar dimelia, Ultrasound antenatal screen abnormal, Ultrasound antenatal screen normal, Ultrasound foetal abnormal, Umbilical artery hypoplasia, Umbilical artery vascular resistance increased, Umbilical cord abnormality, Umbilical cord around neck, Umbilical cord compression, Umbilical cord cyst, Umbilical cord haemorrhage, Umbilical cord occlusion, Umbilical cord prolapse, Umbilical cord short, Umbilical cord thrombosis, Umbilical cord vascular disorder, Umbilical discharge, Umbilical granuloma, Umbilical malformation, Umbilical sepsis, Unicuspid aortic valve, Unintended pregnancy, Univentricular heart, Unstable foetal lie, Unwanted pregnancy, Urachal abnormality, Urea cycle disorder, Ureteric atresia, Urethral atresia, Urethral valves, Urinary tract infection neonatal, Urinary tract malformation, Urofacial syndrome, Usher's syndrome, Uterine adhesions, Uterine aplasia, Uterine artery embolisation, Uterine atony, Uterine cervix canal atresia, Uterine cervix hypoplasia, Uterine cervix stenosis, Uterine compression sutures, Uterine contractions abnormal, Uterine contractions during pregnancy, Uterine dehiscence, Uterine diverticulum, Uterine hyperstimulation, Uterine hypertonus, Uterine hypokinesia, Uterine hypoplasia, Uterine hypotonus, Uterine inversion, Uterine irritability, Uterine malposition, Uterine rupture, Uterine scar, Uterine scar diverticulum, Uterine tachysystole, Uvula aplasia, VACTERL syndrome, VEXAS syndrome, VKORC1 gene polymorphism, Vacuum aspiration, Vacuum extractor delivery, Vaginal atresia, Vaginal hypoplasia, Vaginal septum, Vaginal tamponade, Vallecular cyst, Vanishing twin syndrome, Varicose veins vaginal, Vasa praevia, Vascular endothelial growth factor

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Safety Topic	Preferred Term
	overexpression, Vascular malformation, Vascular rings and slings, Vein of Galen aneurysmal malformation, Velo-cardio-facial syndrome, Venous angioma of brain, Venous thrombosis in pregnancy, Venous thrombosis neonatal, Ventricular hypoplasia, Ventricular septal defect, Ventricular septal defect repair, Vertebral artery fenestration, Vertebral artery hypoplasia, Vertical talus, Very long-chain acyl-coenzyme A dehydrogenase deficiency, Vesicoamniotic shunt, Vestibulocerebellar syndrome, Virilism foetal, Vision abnormal neonatal, Vitello-intestinal duct remnant, Von Hippel-Lindau disease, Von Willebrand's disease, Von Willebrand's disease gene carrier, Vulvovaginal injury, WNT4 deficiency, WT1 gene mutation, Waardenburg syndrome, Wagner's disease, Weaver syndrome, Weight decrease neonatal, Weill-Marchesani syndrome, Welander distal myopathy, Werner's syndrome, Wildervanck syndrome, Williams syndrome, Winchester syndrome, Wiskott-Aldrich syndrome, Wolf-Hirschhorn syndrome, Wolff-Parkinson-White syndrome congenital, Wolfram syndrome, Woodhouse-Sakati syndrome, Wyburn Mason's syndrome, X-linked chromosomal disorder, X-linked intellectual disability, Siderius type, X-linked lymphoproliferative syndrome, XXX syndrome, XXXY syndrome, XXYY syndrome, XYY syndrome, Xeroderma pigmentosum, Y-linked chromosomal disorder, Young's syndrome, ZRSR2 gene mutation, Zeichi-Ceide syndrome, Zhu-Tokita-Takenouchi-Kim syndrome, Zika virus associated birth defect, Zika virus associated microencephaly, Zika virus associated ocular birth defect
Second Primary Malignancies	5q minus syndrome, ACTH-producing pituitary tumour, APUDoma, Abdominal neoplasm, Abdominal wall neoplasm, Abdominal wall neoplasm malignant, Acinar cell carcinoma of pancreas, Acinic cell carcinoma of salivary gland, Acral lentiginous melanoma, Acral lentiginous melanoma stage I, Acral lentiginous melanoma stage II, Acral lentiginous melanoma stage III, Acral lentiginous melanoma stage IV, Acute bilineal leukaemia, Acute biphenotypic leukaemia, Acute erythroid leukaemia, Acute leukaemia, Acute leukaemia in remission, Acute lymphocytic leukaemia, Acute lymphocytic leukaemia (in remission), Acute lymphocytic leukaemia recurrent, Acute lymphocytic leukaemia refractory, Acute megakaryocytic leukaemia, Acute megakaryocytic leukaemia (in remission), Acute monocytic leukaemia, Acute monocytic leukaemia (in remission), Acute myeloid leukaemia, Acute myeloid leukaemia (in remission), Acute myeloid leukaemia recurrent, Acute myeloid leukaemia refractory, Acute myelomonocytic leukaemia, Acute promyelocytic leukaemia, Acute undifferentiated leukaemia, Adenocarcinoid tumour of the appendix, Adenocarcinoma, Adenocarcinoma gastric, Adenocarcinoma metastatic, Adenocarcinoma of appendix, Adenocarcinoma of colon, Adenocarcinoma of salivary gland, Adenocarcinoma of the cervix, Adenocarcinoma pancreas, Adenoid cystic carcinoma, Adenoid cystic carcinoma of salivary gland, Adenomatous polyposis coli, Adenomyoepithelioma of breast, Adenosquamous carcinoma of the cervix, Adenosquamous carcinoma of vagina, Adenosquamous cell carcinoma, Adenosquamous cell lung cancer, Adenosquamous cell lung cancer recurrent, Adenosquamous cell lung cancer stage 0, Adenosquamous cell lung cancer stage I, Adenosquamous cell lung cancer stage II, Adenosquamous cell lung cancer stage III, Adenosquamous cell lung cancer stage IV, Adrenal cyst, Adrenal gland cancer, Adrenal gland cancer metastatic, Adrenal neoplasm, Adrenocortical carcinoma, Adult T-cell lymphoma/leukaemia, Adult T-cell lymphoma/leukaemia recurrent, Adult T-cell lymphoma/leukaemia refractory, Adult T-cell lymphoma/leukaemia stage I, Adult T-cell lymphoma/leukaemia stage II, Adult T-cell lymphoma/leukaemia stage III, Adult T-cell lymphoma/leukaemia stage IV, Advanced systemic mastocytosis, Aesthesioneuroblastoma, Aleukaemic leukaemia, Alveolar rhabdomyosarcoma, Alveolar soft part sarcoma, Alveolar soft part sarcoma metastatic, Alveolar soft part sarcoma recurrent, Ameloblastic carcinoma, Ameloblastic fibrosarcoma, Ampullary polyp, Anal cancer, Anal cancer metastatic, Anal cancer recurrent, Anal cancer stage 0, Anal cancer stage I, Anal cancer stage II, Anal cancer stage III, Anal cancer stage IV, Anal neoplasm, Anal squamous cell carcinoma, Anaplastic ganglioglioma, Anaplastic large cell lymphoma T- and null-cell types, Anaplastic large cell lymphoma T- and null-cell types recurrent, Anaplastic large cell lymphoma T- and null-cell types refractory, Anaplastic large cell lymphoma T- and null-cell types stage I, Anaplastic large cell lymphoma T- and null-cell types stage II, Anaplastic large cell lymphoma T- and null-cell types stage III, Anaplastic large cell lymphoma T- and null-cell types stage IV, Anaplastic large-cell lymphoma, Anaplastic meningioma, Anaplastic thyroid cancer, Angiocentric glioma, Angiocentric lymphoma, Angiocentric lymphoma recurrent, Angiocentric lymphoma refractory, Angiocentric lymphoma stage I, Angiocentric lymphoma stage II, Angiocentric lymphoma stage III, Angiocentric lymphoma stage IV, Angioimmunoblastic T-cell lymphoma, Angioimmunoblastic T-cell lymphoma recurrent, Angioimmunoblastic T-cell lymphoma refractory, Angioimmunoblastic T-cell lymphoma stage I,

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Safety Topic	Preferred Term
	Angioimmunoblastic T-cell lymphoma stage II, Angioimmunoblastic T-cell lymphoma stage III, Angioimmunoblastic T-cell lymphoma stage IV, Angiosarcoma, Angiosarcoma metastatic, Angiosarcoma non-metastatic, Angiosarcoma recurrent, Apocrine breast carcinoma, Appendix cancer, Appendix cancer metastatic, Astroblastoma, Astrocytoma, Astrocytoma malignant, Atypical fibroxanthoma, Atypical teratoid/rhabdoid tumour of CNS, B precursor type acute leukaemia, B-cell lymphoma, B-cell lymphoma recurrent, B-cell lymphoma refractory, B-cell lymphoma stage I, B-cell lymphoma stage II, B-cell lymphoma stage III, B-cell lymphoma stage IV, B-cell lymphoma unclassifiable, B-cell prolymphocytic leukaemia, B-cell small lymphocytic lymphoma, B-cell small lymphocytic lymphoma recurrent, B-cell small lymphocytic lymphoma refractory, B-cell small lymphocytic lymphoma stage I, B-cell small lymphocytic lymphoma stage II, B-cell small lymphocytic lymphoma stage III, B-cell small lymphocytic lymphoma stage IV, B-cell type acute leukaemia, B-cell unclassifiable lymphoma high grade, B-cell unclassifiable lymphoma low grade, Basal cell carcinoma, Basal cell carcinoma metastatic, Basal cell naevus syndrome, Basosquamous carcinoma, Basosquamous carcinoma of skin, Benign lymph node neoplasm, Benign spleen tumour, Bile duct adenocarcinoma, Bile duct adenosquamous carcinoma, Bile duct cancer, Bile duct cancer recurrent, Bile duct cancer stage 0, Bile duct cancer stage I, Bile duct cancer stage II, Bile duct cancer stage III, Bile duct cancer stage IV, Bile duct squamous cell carcinoma, Biliary cancer metastatic, Biliary neoplasm, Bing-Neel syndrome, Biphasic mesothelioma, Bladder adenocarcinoma recurrent, Bladder adenocarcinoma stage 0, Bladder adenocarcinoma stage I, Bladder adenocarcinoma stage II, Bladder adenocarcinoma stage III, Bladder adenocarcinoma stage IV, Bladder adenocarcinoma stage unspecified, Bladder cancer, Bladder cancer recurrent, Bladder cancer stage 0, with cancer in situ, Bladder cancer stage 0, without cancer in situ, Bladder cancer stage I, with cancer in situ, Bladder cancer stage I, without cancer in situ, Bladder cancer stage II, Bladder cancer stage III, Bladder cancer stage IV, Bladder neoplasm, Bladder squamous cell carcinoma recurrent, Bladder squamous cell carcinoma stage 0, Bladder squamous cell carcinoma stage I, Bladder squamous cell carcinoma stage II, Bladder squamous cell carcinoma stage III, Bladder squamous cell carcinoma stage IV, Bladder squamous cell carcinoma stage unspecified, Bladder transitional cell carcinoma, Bladder transitional cell carcinoma metastatic, Bladder transitional cell carcinoma recurrent, Bladder transitional cell carcinoma stage 0, Bladder transitional cell carcinoma stage I, Bladder transitional cell carcinoma stage II, Bladder transitional cell carcinoma stage III, Bladder transitional cell carcinoma stage IV, Blast cell crisis, Blast cell proliferation, Blast crisis in myelogenous leukaemia, Blastic plasmacytoid dendritic cell neoplasia, Bone cancer, Bone cancer metastatic, Bone giant cell tumour, Bone giant cell tumour malignant, Bone marrow leukaemic cell infiltration, Bone marrow tumour cell infiltration, Bone neoplasm, Bone sarcoma, Borderline mucinous tumour of ovary, Borderline ovarian tumour, Borderline serous tumour of ovary, Bowen's disease, Brain cancer metastatic, Brain neoplasm, Brain neoplasm malignant, Brain sarcoma, Brain stem glioma, Brain teratoma, Breast angiosarcoma, Breast angiosarcoma metastatic, Breast cancer, Breast cancer female, Breast cancer in situ, Breast cancer male, Breast cancer metastatic, Breast cancer recurrent, Breast cancer stage I, Breast cancer stage II, Breast cancer stage III, Breast cancer stage IV, Breast implant-associated anaplastic large cell lymphoma, Breast neoplasm, Breast sarcoma, Breast sarcoma metastatic, Breast sarcoma recurrent, Brenner tumour, Bronchial carcinoma, Bronchial neoplasm, Bronchioloalveolar carcinoma, Burkitt's leukaemia, Burkitt's lymphoma, Burkitt's lymphoma recurrent, Burkitt's lymphoma refractory, Burkitt's lymphoma stage I, Burkitt's lymphoma stage II, Burkitt's lymphoma stage III, Burkitt's lymphoma stage IV, Buschke-Lowenstein's tumour, CNS germinoma, Cancer in remission, Cancer with a high tumour mutational burden, Carcinogenic effect in offspring, Carcinoid tumour, Carcinoid tumour in the large intestine, Carcinoid tumour of the gastrointestinal tract, Carcinoid tumour of the liver, Carcinoid tumour of the mesentery, Carcinoid tumour of the ovary, Carcinoid tumour of the pancreas, Carcinoid tumour of the prostate, Carcinoid tumour of the small bowel, Carcinoid tumour of the stomach, Carcinoid tumour pulmonary, Carcinoma ex-pleomorphic adenoma, Carcinoma in situ, Carcinoma in situ of eye, Carcinoma in situ of penis, Carcinoma in situ of skin, Carcinoma in situ of trachea, Cardiac neoplasm malignant, Cardiac neoplasm unspecified, Cardiac teratoma, Cartilage neoplasm, Castleman's disease, Central nervous system dermoid tumour, Central nervous system leukaemia, Central nervous system lymphoma, Central nervous system melanoma, Central nervous system neoplasm, Central nervous system neuroblastoma, Cerebellar tumour, Cerebellopontine angle tumour, Cervix cancer metastatic, Cervix carcinoma, Cervix carcinoma recurrent, Cervix carcinoma stage 0, Cervix carcinoma stage I, Cervix carcinoma stage II, Cervix carcinoma stage III, Cervix carcinoma stage IV, Cervix

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Safety Topic	Preferred Term
	neoplasm, Chest wall tumour, Chloroma, Chloroma (in remission), Cholangiocarcinoma, Cholangiosarcoma, Chondrosarcoma, Chondrosarcoma metastatic, Chondrosarcoma recurrent, Chordoma, Choriocarcinoma, Choroid melanoma, Choroid neoplasm, Choroid plexus carcinoma, Chromophobe renal cell carcinoma, Chronic eosinophilic leukaemia, Chronic leukaemia, Chronic leukaemia in remission, Chronic lymphocytic leukaemia, Chronic lymphocytic leukaemia (in remission), Chronic lymphocytic leukaemia recurrent, Chronic lymphocytic leukaemia refractory, Chronic lymphocytic leukaemia stage 0, Chronic lymphocytic leukaemia stage 1, Chronic lymphocytic leukaemia stage 2, Chronic lymphocytic leukaemia stage 3, Chronic lymphocytic leukaemia stage 4, Chronic lymphocytic leukaemia transformation, Chronic myeloid leukaemia, Chronic myeloid leukaemia (in remission), Chronic myeloid leukaemia recurrent, Chronic myeloid leukaemia transformation, Chronic myelomonocytic leukaemia, Chronic myelomonocytic leukaemia (in remission), Chronic myelomonocytic leukaemia with N-ras gene mutation, Ciliary body melanoma, Clear cell carcinoma of cervix, Clear cell endometrial carcinoma, Clear cell papillary renal cell carcinoma, Clear cell renal cell carcinoma, Clear cell sarcoma of soft tissue, Clear cell sarcoma of the kidney, Colon cancer, Colon cancer metastatic, Colon cancer recurrent, Colon cancer stage 0, Colon cancer stage I, Colon cancer stage II, Colon cancer stage III, Colon cancer stage IV, Colon neoplasm, Colorectal adenocarcinoma, Colorectal cancer, Colorectal cancer metastatic, Colorectal cancer recurrent, Colorectal cancer stage I, Colorectal cancer stage II, Colorectal cancer stage III, Colorectal cancer stage IV, Colorectal carcinoma stage 0, Colorectal neoplasm, Composite lymphoma, Congenital fibrosarcoma, Congenital malignant neoplasm, Congenital neoplasm, Congenital retinoblastoma, Congenital teratoma, Conjunctival melanoma, Conjunctival neoplasm, Conjunctival primary acquired melanosis, Connective tissue neoplasm, Cranial nerve neoplasm, Craniopharyngioma malignant, Cronkhite-Canada syndrome, Cutaneous B-cell lymphoma, Cutaneous T-cell lymphoma, Cutaneous T-cell lymphoma recurrent, Cutaneous T-cell lymphoma refractory, Cutaneous T-cell lymphoma stage I, Cutaneous T-cell lymphoma stage II, Cutaneous T-cell lymphoma stage III, Cutaneous T-cell lymphoma stage IV, Cutaneous lymphoma, Cystadenocarcinoma ovary, Cystadenocarcinoma pancreas, Dedifferentiated liposarcoma, Denys-Drash syndrome, Dermatofibrosarcoma protuberans, Dermatofibrosarcoma protuberans metastatic, Desmoplastic melanoma, Desmoplastic mesothelioma, Desmoplastic small round cell tumour, Diaphragm neoplasm, Diffuse large B-cell lymphoma, Diffuse large B-cell lymphoma recurrent, Diffuse large B-cell lymphoma refractory, Diffuse large B-cell lymphoma stage I, Diffuse large B-cell lymphoma stage II, Diffuse large B-cell lymphoma stage III, Diffuse large B-cell lymphoma stage IV, Disseminated large cell lymphoma, Double hit lymphoma, Ductal adenocarcinoma of pancreas, Duodenal neoplasm, Dysplastic naevus syndrome, Ear neoplasm, Ear neoplasm malignant, Eccrine carcinoma, Embryonal rhabdomyosarcoma, Endocrine neoplasm, Endocrine neoplasm malignant, Endometrial adenocarcinoma, Endometrial cancer, Endometrial cancer metastatic, Endometrial cancer recurrent, Endometrial cancer stage 0, Endometrial cancer stage I, Endometrial cancer stage II, Endometrial cancer stage III, Endometrial cancer stage IV, Endometrial neoplasm, Endometrial sarcoma, Endometrial sarcoma metastatic, Endometrial sarcoma recurrent, Endometrial stromal sarcoma, Endotheliomatosis, Enteropathy-associated T-cell lymphoma, Eosinophilic leukaemia, Ependymoma, Ependymoma malignant, Epidermal naevus syndrome, Epididymal cancer, Epididymal neoplasm, Epiglottic cancer, Epiglottic neoplasm, Epithelioid mesothelioma, Epithelioid sarcoma, Epithelioid sarcoma metastatic, Epithelioid sarcoma recurrent, Epstein Barr virus positive mucocutaneous ulcer, Epstein-Barr virus associated lymphoma, Epstein-Barr virus associated lymphoproliferative disorder, Erdheim-Chester disease, Erythraemic myelosis (in remission), Erythroplasia, Erythroplasia of lip, Erythroplasia of penis, Erythroplasia of vulva, Essential thrombocythaemia, Ewing's sarcoma, Ewing's sarcoma metastatic, Ewing's sarcoma recurrent, Ewing-like sarcoma, External ear neoplasm malignant, Extra-osseous Ewing's sarcoma, Extra-osseous Ewing's sarcoma metastatic, Extra-osseous Ewing's sarcoma recurrent, Extradural neoplasm, Extragonadal primary embryonal carcinoma, Extragonadal primary germ cell tumour, Extragonadal primary germ cell tumour mixed, Extragonadal primary germ cell tumour mixed stage I, Extragonadal primary germ cell tumour mixed stage II, Extragonadal primary germ cell tumour mixed stage III, Extragonadal primary malignant teratoma, Extragonadal primary non-seminoma, Extragonadal primary non-seminoma stage I, Extragonadal primary non-seminoma stage II, Extragonadal primary non-seminoma stage III, Extragonadal primary non-seminoma stage IV, Extragonadal primary seminoma (pure), Extragonadal primary seminoma (pure) stage I, Extragonadal primary seminoma (pure) stage II, Extragonadal primary

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Safety Topic	Preferred Term
	seminoma (pure) stage III, Extragonadal primary seminoma (pure) stage IV, Extramammary Paget's disease, Extranodal marginal zone B-cell lymphoma (BALT type), Extranodal marginal zone B-cell lymphoma (MALT type), Extranodal marginal zone B-cell lymphoma (MALT type) recurrent, Extranodal marginal zone B-cell lymphoma (MALT type) refractory, Extranodal marginal zone B-cell lymphoma (MALT type) stage I, Extranodal marginal zone B-cell lymphoma (MALT type) stage II, Extranodal marginal zone B-cell lymphoma (MALT type) stage III, Extranodal marginal zone B-cell lymphoma (MALT type) stage IV, Extraocular retinoblastoma, Extraskeletal chondrosarcoma metastatic, Extraskeletal chondrosarcoma recurrent, Extraskeletal myxoid chondrosarcoma, Extraskeletal osteosarcoma, Extraskeletal osteosarcoma metastatic, Extraskeletal osteosarcoma recurrent, Eyelid tumour, Fallopian tube cancer, Fallopian tube cancer metastatic, Fallopian tube cancer stage I, Fallopian tube cancer stage II, Fallopian tube cancer stage III, Fallopian tube cancer stage IV, Fallopian tube neoplasm, Familial acromegaly, Familial haemophagocytic lymphohistiocytosis, Familial medullary thyroid cancer, Female reproductive neoplasm, Female reproductive tract carcinoma in situ, Fibrosarcoma, Fibrosarcoma metastatic, Follicle centre lymphoma diffuse small cell lymphoma, Follicle centre lymphoma diffuse small cell lymphoma recurrent, Follicle centre lymphoma diffuse small cell lymphoma refractory, Follicle centre lymphoma diffuse small cell lymphoma stage I, Follicle centre lymphoma diffuse small cell lymphoma stage II, Follicle centre lymphoma diffuse small cell lymphoma stage III, Follicle centre lymphoma diffuse small cell lymphoma stage IV, Follicle centre lymphoma, follicular grade I, II, III, Follicle centre lymphoma, follicular grade I, II, III recurrent, Follicle centre lymphoma, follicular grade I, II, III refractory, Follicle centre lymphoma, follicular grade I, II, III stage I, Follicle centre lymphoma, follicular grade I, II, III stage II, Follicle centre lymphoma, follicular grade I, II, III stage III, Follicle centre lymphoma, follicular grade I, II, III stage IV, Follicular dendritic cell sarcoma, Follicular lymphoma, Follicular lymphoma recurrent, Follicular lymphoma refractory, Follicular lymphoma stage I, Follicular lymphoma stage II, Follicular lymphoma stage III, Follicular lymphoma stage IV, Follicular thyroid cancer, Frasier syndrome, Gallbladder adenocarcinoma, Gallbladder adenosquamous carcinoma, Gallbladder cancer, Gallbladder cancer metastatic, Gallbladder cancer recurrent, Gallbladder cancer stage 0, Gallbladder cancer stage I, Gallbladder cancer stage II, Gallbladder cancer stage III, Gallbladder cancer stage IV, Gallbladder neoplasm, Gallbladder squamous cell carcinoma, Gammopathy, Ganglioglioma, Ganglioneuroblastoma, Gastric cancer, Gastric cancer recurrent, Gastric cancer stage 0, Gastric cancer stage I, Gastric cancer stage II, Gastric cancer stage III, Gastric cancer stage IV, Gastric neoplasm, Gastric neuroendocrine carcinoma, Gastric sarcoma, Gastrinoma, Gastrinoma malignant, Gastroenteropancreatic neuroendocrine tumour disease, Gastrointestinal adenocarcinoma, Gastrointestinal cancer metastatic, Gastrointestinal carcinoma, Gastrointestinal carcinoma in situ, Gastrointestinal lymphoma, Gastrointestinal melanoma, Gastrointestinal neoplasm, Gastrointestinal neuroendocrine carcinoma, Gastrointestinal stromal tumour, Gastrointestinal submucosal tumour, Gastrooesophageal cancer, Gastrooesophageal cancer recurrent, Genital cancer male, Genital cancer male in situ, Genital cyst, Genital neoplasm malignant female, Genitourinary melanoma, Genitourinary tract neoplasm, Germ cell cancer, Germ cell cancer metastatic, Germ cell neoplasm, Gestational trophoblastic tumour, Gingival cancer, Glioblastoma, Glioblastoma multiforme, Glioma, Gliomatosis cerebri, Glioneuronal tumour, Gliosarcoma, Glomangiopericytoma, Glottis carcinoma, Glucagonoma, Good syndrome, Granular cell tumour, Granulosa cell tumour of the testis, Grey zone lymphoma, Growing teratoma syndrome, Growth hormone-producing pituitary tumour, HER2 low breast cancer, HER2 mutant non-small cell lung cancer, HER2 negative breast cancer, HER2 positive biliary tract cancer, HER2 positive bladder cancer, HER2 positive breast cancer, HER2 positive cervix cancer, HER2 positive colorectal cancer, HER2 positive endometrial cancer, HER2 positive gastric cancer, HER2 positive ovarian cancer, HER2 positive pancreatic carcinoma, HER2 positive salivary gland cancer, Haemangioma of spleen, Haemangiopericytoma, Haemangiopericytoma of meninges, Haematological cyst, Haematological malignancy, Haematological neoplasm, Haematopoietic neoplasm, Hairy cell leukaemia, Hairy cell leukaemia recurrent, Head and neck cancer, Head and neck cancer metastatic, Head and neck cancer stage I, Head and neck cancer stage II, Head and neck cancer stage III, Head and neck cancer stage IV, Heavy chain disease, Hepatic angiosarcoma, Hepatic cancer, Hepatic cancer metastatic, Hepatic cancer recurrent, Hepatic cancer stage I, Hepatic cancer stage II, Hepatic cancer stage III, Hepatic cancer stage IV, Hepatic neoplasm, Hepatic neuroendocrine tumour, Hepatic sarcoma, Hepatobiliary cancer, Hepatobiliary cancer in situ, Hepatobiliary neoplasm, Hepatoblastoma, Hepatoblastoma recurrent,

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Safety Topic	Preferred Term
	Hepatocellular carcinoma, Hepatosplenic T-cell lymphoma, Hereditary leiomyomatosis renal cell carcinoma, Hereditary non-polyposis colorectal cancer syndrome, Hereditary papillary renal carcinoma, Hidradenocarcinoma, High grade B-cell lymphoma Burkitt-like lymphoma, High grade B-cell lymphoma Burkitt-like lymphoma recurrent, High grade B-cell lymphoma Burkitt-like lymphoma refractory, High grade B-cell lymphoma Burkitt-like lymphoma stage I, High grade B-cell lymphoma Burkitt-like lymphoma stage II, High grade B-cell lymphoma Burkitt-like lymphoma stage III, High grade B-cell lymphoma Burkitt-like lymphoma stage IV, High grade B-cell lymphoma recurrent, High grade B-cell lymphoma refractory, High-grade B-cell lymphoma, Histiocytic medullary reticulosis, Histiocytic necrotising lymphadenitis, Histiocytic sarcoma, Histiocytosis, Histiocytosis-lymphadenopathy plus syndrome, Hodgkin's disease, Hodgkin's disease lymphocyte depletion stage I site unspecified, Hodgkin's disease lymphocyte depletion stage I subdiaphragm, Hodgkin's disease lymphocyte depletion stage I supradiaphragm, Hodgkin's disease lymphocyte depletion stage II site unspecified, Hodgkin's disease lymphocyte depletion stage II subdiaphragm, Hodgkin's disease lymphocyte depletion stage II supradiaphragm, Hodgkin's disease lymphocyte depletion type recurrent, Hodgkin's disease lymphocyte depletion type refractory, Hodgkin's disease lymphocyte depletion type stage III, Hodgkin's disease lymphocyte depletion type stage IV, Hodgkin's disease lymphocyte depletion type stage unspecified, Hodgkin's disease lymphocyte predominance stage I site unspec, Hodgkin's disease lymphocyte predominance stage I subdiaphragm, Hodgkin's disease lymphocyte predominance stage I supradiaphragm, Hodgkin's disease lymphocyte predominance stage II site unspec, Hodgkin's disease lymphocyte predominance stage II subdiaphragm, Hodgkin's disease lymphocyte predominance stage II supradiaphragm, Hodgkin's disease lymphocyte predominance type recurrent, Hodgkin's disease lymphocyte predominance type refractory, Hodgkin's disease lymphocyte predominance type stage III, Hodgkin's disease lymphocyte predominance type stage IV, Hodgkin's disease lymphocyte predominance type stage unspecified, Hodgkin's disease mixed cellularity recurrent, Hodgkin's disease mixed cellularity refractory, Hodgkin's disease mixed cellularity stage I site unspecified, Hodgkin's disease mixed cellularity stage I subdiaphragmatic, Hodgkin's disease mixed cellularity stage I supradiaphragmatic, Hodgkin's disease mixed cellularity stage II subdiaphragmatic, Hodgkin's disease mixed cellularity stage II supradiaphragmatic, Hodgkin's disease mixed cellularity stage III, Hodgkin's disease mixed cellularity stage IV, Hodgkin's disease mixed cellularity stage unspecified, Hodgkin's disease nodular sclerosis, Hodgkin's disease nodular sclerosis recurrent, Hodgkin's disease nodular sclerosis refractory, Hodgkin's disease nodular sclerosis stage I, Hodgkin's disease nodular sclerosis stage II, Hodgkin's disease nodular sclerosis stage III, Hodgkin's disease nodular sclerosis stage IV, Hodgkin's disease recurrent, Hodgkin's disease refractory, Hodgkin's disease stage I, Hodgkin's disease stage II, Hodgkin's disease stage III, Hodgkin's disease stage IV, Hodgkin's disease unclassifiable, Homologous recombination deficiency positive advanced ovarian cancer, Hormone receptor negative HER2 positive breast cancer, Hormone receptor positive HER2 negative breast cancer, Hormone receptor positive breast cancer, Hormone refractory breast cancer, Hormone-dependent prostate cancer, Hormone-refractory prostate cancer, Hormone-secreting ovarian tumour, Huerthle cell carcinoma, Hypergammaglobulinaemia benign monoclonal, Hypopharyngeal cancer, Hypopharyngeal cancer recurrent, Hypopharyngeal cancer stage 0, Hypopharyngeal cancer stage I, Hypopharyngeal cancer stage II, Hypopharyngeal cancer stage III, Hypopharyngeal cancer stage IV, Hypopharyngeal neoplasm, Immune reconstitution inflammatory syndrome associated Kaposi's sarcoma, Immunoblastic lymphoma, Indolent systemic mastocytosis, Inflammatory carcinoma of breast recurrent, Inflammatory carcinoma of breast stage III, Inflammatory carcinoma of breast stage IV, Inflammatory carcinoma of the breast, Inflammatory malignant fibrous histiocytoma, Inflammatory myofibroblastic tumour, Insulinoma, Intestinal T-cell lymphoma recurrent, Intestinal T-cell lymphoma refractory, Intestinal T-cell lymphoma stage I, Intestinal T-cell lymphoma stage II, Intestinal T-cell lymphoma stage III, Intestinal T-cell lymphoma stage IV, Intestinal adenocarcinoma, Intracholecystic papillary neoplasm, Intracranial germ cell tumour, Intracranial meningioma malignant, Intraductal papillary breast neoplasm, Intraductal papillary mucinous neoplasm, Intraductal papillary-mucinous carcinoma of pancreas, Intraductal proliferative breast lesion, Intraosseous angioma, Intraosseous meningioma, Invasive breast carcinoma, Invasive ductal breast carcinoma, Invasive lobular breast carcinoma, Invasive papillary breast carcinoma, Iris melanoma, Iris neoplasm, Joint neoplasm, Juvenile chronic myelomonocytic leukaemia, Juvenile polyposis syndrome, Juvenile xanthogranuloma, Kaposi's sarcoma, Kaposi's sarcoma AIDS related, Kaposi's sarcoma classical type, Kaposiform haemangioendothelioma,

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Safety Topic	Preferred Term
	Keratinising squamous cell carcinoma of nasopharynx, Keratoacanthoma, Lacrimal duct neoplasm, Lacrimal gland neoplasm, Langerhans cell sarcoma, Langerhans' cell histiocytosis, Large cell lung cancer, Large cell lung cancer metastatic, Large cell lung cancer recurrent, Large cell lung cancer stage 0, Large cell lung cancer stage I, Large cell lung cancer stage II, Large cell lung cancer stage III, Large cell lung cancer stage IV, Large granular lymphocytosis, Laryngeal cancer, Laryngeal cancer metastatic, Laryngeal cancer recurrent, Laryngeal cancer stage 0, Laryngeal cancer stage I, Laryngeal cancer stage II, Laryngeal cancer stage III, Laryngeal cancer stage IV, Laryngeal neoplasm, Laryngeal squamous cell carcinoma, Leiomyosarcoma, Leiomyosarcoma metastatic, Leiomyosarcoma recurrent, Lentigo maligna, Lentigo maligna recurrent, Lentigo maligna stage I, Lentigo maligna stage II, Lentigo maligna stage III, Lentigo maligna stage IV, Leptomeningeal myelomatosis, Leukaemia, Leukaemia basophilic, Leukaemia cutis, Leukaemia granulocytic, Leukaemia in remission, Leukaemia monocytic, Leukaemia recurrent, Leukaemic cardiac infiltration, Leukaemic infiltration, Leukaemic infiltration extramedullary, Leukaemic infiltration gingiva, Leukaemic infiltration hepatic, Leukaemic infiltration ovary, Leukaemic infiltration pulmonary, Leukaemic infiltration renal, Leukaemic lymphoma, Leukaemic retinopathy, Leukoerythroblastosis, Leydig cell tumour of the testis, Light chain disease, Lineage switch leukaemia, Linitis plastica, Lip and/or oral cavity cancer, Lip and/or oral cavity cancer recurrent, Lip and/or oral cavity cancer stage 0, Lip and/or oral cavity cancer stage I, Lip and/or oral cavity cancer stage II, Lip and/or oral cavity cancer stage III, Lip and/or oral cavity cancer stage IV, Lip neoplasm, Lip neoplasm malignant stage unspecified, Lip squamous cell carcinoma, Liposarcoma, Liposarcoma metastatic, Liposarcoma recurrent, Liposclerosing myxofibrous tumour, Liver carcinoma ruptured, Lobular breast carcinoma in situ, Lung adenocarcinoma, Lung adenocarcinoma recurrent, Lung adenocarcinoma stage 0, Lung adenocarcinoma stage I, Lung adenocarcinoma stage II, Lung adenocarcinoma stage III, Lung adenocarcinoma stage IV, Lung cancer metastatic, Lung carcinoma cell type unspecified recurrent, Lung carcinoma cell type unspecified stage 0, Lung carcinoma cell type unspecified stage I, Lung carcinoma cell type unspecified stage II, Lung carcinoma cell type unspecified stage III, Lung carcinoma cell type unspecified stage IV, Lung infiltration malignant, Lung neoplasm, Lung neoplasm malignant, Lung squamous cell carcinoma metastatic, Lung squamous cell carcinoma recurrent, Lung squamous cell carcinoma stage 0, Lung squamous cell carcinoma stage I, Lung squamous cell carcinoma stage II, Lung squamous cell carcinoma stage III, Lung squamous cell carcinoma stage IV, Lymphangiosarcoma, Lymphatic system neoplasm, Lymphocytic leukaemia, Lymphocytic lymphoma, Lymphoid leukaemia (in remission), Lymphoma, Lymphoma AIDS related, Lymphoma transformation, Lymphoplasmacytoid lymphoma/immunocytoma, Lymphoplasmacytoid lymphoma/immunocytoma recurrent, Lymphoplasmacytoid lymphoma/immunocytoma refractory, Lymphoplasmacytoid lymphoma/immunocytoma stage I, Lymphoplasmacytoid lymphoma/immunocytoma stage II, Lymphoplasmacytoid lymphoma/immunocytoma stage III, Lymphoplasmacytoid lymphoma/immunocytoma stage IV, Lymphoproliferative disorder, Lymphoproliferative disorder in remission, Male reproductive tract neoplasm, Malignant anorectal neoplasm, Malignant blue naevus, Malignant central nervous system neoplasm, Malignant connective tissue neoplasm, Malignant cranial nerve neoplasm, Malignant fibrous histiocytoma, Malignant fibrous histiocytoma metastatic, Malignant fibrous histiocytoma of bone, Malignant fibrous histiocytoma recurrent, Malignant gastric ulcer, Malignant genitourinary tract neoplasm, Malignant giant cell fibrous histiocytoma, Malignant glioma, Malignant haemangiopericytoma, Malignant haemangiopericytoma metastatic, Malignant haemangiopericytoma recurrent, Malignant histiocytosis, Malignant hydatidiform mole, Malignant joint neoplasm, Malignant lymphoid neoplasm, Malignant lymphoma unclassifiable high grade, Malignant lymphoma unclassifiable low grade, Malignant mast cell neoplasm, Malignant mediastinal neoplasm, Malignant melanoma, Malignant melanoma in situ, Malignant melanoma of eyelid, Malignant melanoma of sites other than skin, Malignant melanoma stage I, Malignant melanoma stage II, Malignant melanoma stage III, Malignant melanoma stage IV, Malignant meningioma metastatic, Malignant mesenchymoma, Malignant mesenchymoma metastatic, Malignant mesenchymoma recurrent, Malignant mesenteric neoplasm, Malignant middle ear neoplasm, Malignant muscle neoplasm, Malignant neoplasm of ampulla of Vater, Malignant neoplasm of choroid, Malignant neoplasm of conjunctiva, Malignant neoplasm of cornea, Malignant neoplasm of eye, Malignant neoplasm of eyelid, Malignant neoplasm of islets of Langerhans, Malignant neoplasm of lacrimal duct, Malignant neoplasm of lacrimal gland, Malignant neoplasm of orbit, Malignant neoplasm of paraurethral glands, Malignant neoplasm of placenta, Malignant neoplasm of pleura, Malignant

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Safety Topic	Preferred Term
	neoplasm of pleura metastatic, Malignant neoplasm of renal pelvis, Malignant neoplasm of retina, Malignant neoplasm of seminal vesicle, Malignant neoplasm of spermatic cord, Malignant neoplasm of spinal cord, Malignant neoplasm of thorax, Malignant neoplasm of thymus, Malignant neoplasm of unknown primary site, Malignant neoplasm of uterine adnexa, Malignant neoplasm oligoprogression, Malignant neoplasm papilla of Vater, Malignant neoplasm progression, Malignant nervous system neoplasm, Malignant nipple neoplasm, Malignant nipple neoplasm female, Malignant nipple neoplasm male, Malignant oligodendroglioma, Malignant ovarian cyst, Malignant palate neoplasm, Malignant pericardial neoplasm, Malignant peritoneal neoplasm, Malignant pituitary tumour, Malignant polyp, Malignant respiratory tract neoplasm, Malignant splenic neoplasm, Malignant sweat gland neoplasm, Malignant transformation, Malignant unclassifiable lymphoma, Malignant urinary tract neoplasm, Malignant urinary tract neoplasm metastatic, Mantle cell lymphoma, Mantle cell lymphoma recurrent, Mantle cell lymphoma refractory, Mantle cell lymphoma stage I, Mantle cell lymphoma stage II, Mantle cell lymphoma stage III, Mantle cell lymphoma stage IV, Marginal zone lymphoma, Marginal zone lymphoma recurrent, Marginal zone lymphoma refractory, Marginal zone lymphoma stage I, Marginal zone lymphoma stage II, Marginal zone lymphoma stage III, Marginal zone lymphoma stage IV, Marjolin's ulcer, Marrow hyperplasia, Mastocytic leukaemia, Mastocytoma, Maternal cancer in pregnancy, Mature B-cell type acute leukaemia, Maxillofacial sinus neoplasm, Meckel's cave tumour, Mediastinum neoplasm, Medullary carcinoma of breast, Medullary thyroid cancer, Medulloblastoma, Medulloblastoma recurrent, Melanoma recurrent, Meningeal neoplasm, Meningioma, Meningioma malignant, Mesenteric neoplasm, Mesothelioma, Mesothelioma malignant, Mesothelioma malignant recurrent, Metaplastic breast carcinoma, Metastatic bronchial carcinoma, Metastatic carcinoid tumour, Metastatic carcinoma of the bladder, Metastatic choriocarcinoma, Metastatic gastric cancer, Metastatic glioma, Metastatic glucagonoma, Metastatic lymphoma, Metastatic malignant melanoma, Metastatic mesothelioma, Metastatic neoplasm, Metastatic nervous system neoplasm, Metastatic ocular melanoma, Metastatic renal cell carcinoma, Metastatic salivary gland cancer, Metastatic squamous cell carcinoma, Metastatic uterine cancer, Microsatellite instability cancer, Minimal residual disease, Mismatch repair cancer syndrome, Mixed adenoneuroendocrine carcinoma, Mixed hepatocellular cholangiocarcinoma, Mixed-type liposarcoma, Monoclonal gammopathy, Monocytic leukaemia in remission, Mucinous adenocarcinoma of appendix, Mucinous breast carcinoma, Mucinous cystadenocarcinoma ovary, Mucinous endometrial carcinoma, Mucoepidermoid carcinoma, Mucoepidermoid carcinoma of salivary gland, Mueller's mixed tumour, Muir-Torre syndrome, Multicentric reticulohistiocytosis, Multiple endocrine neoplasia, Multiple endocrine neoplasia Type 1, Multiple endocrine neoplasia Type 2, Multiple endocrine neoplasia Type 2A, Multiple endocrine neoplasia Type 2B, Muscle neoplasm, Musculoskeletal cancer, Myeloblastoma, Myelodysplastic syndrome, Myelodysplastic syndrome transformation, Myelodysplastic syndrome unclassifiable, Myelodysplastic syndrome with excess blasts, Myelodysplastic syndrome with multilineage dysplasia, Myelodysplastic syndrome with ringed sideroblasts, Myelodysplastic syndrome with single lineage dysplasia, Myelofibrosis, Myeloid leukaemia, Myeloid leukaemia in remission, Myeloid metaplasia, Myeloproliferative neoplasm, Myxofibrosarcoma, Myxoid liposarcoma, NTRK gene fusion cancer, NUT midline carcinoma, Naevoid melanoma, Nasal cavity cancer, Nasal neoplasm, Nasal sinus cancer, Nasopharyngeal cancer, Nasopharyngeal cancer metastatic, Nasopharyngeal cancer recurrent, Nasopharyngeal cancer stage 0, Nasopharyngeal cancer stage I, Nasopharyngeal cancer stage II, Nasopharyngeal cancer stage III, Nasopharyngeal cancer stage IV, Nasopharyngeal tumour, Natural killer-cell leukaemia, Natural killer-cell lymphoblastic lymphoma, Neonatal leukaemia, Neonatal neuroblastoma, Neoplasm, Neoplasm malignant, Neoplasm of appendix, Neoplasm of cornea unspecified malignancy, Neoplasm of orbit, Neoplasm of thymus, Neoplasm progression, Neoplasm prostate, Neoplasm recurrence, Neoplasm skin, Nephroblastoma, Nervous system neoplasm, Neuroblastoma, Neuroblastoma recurrent, Neuroectodermal neoplasm, Neuroendocrine breast tumour, Neuroendocrine cancer of the prostate metastatic, Neuroendocrine carcinoma, Neuroendocrine carcinoma metastatic, Neuroendocrine carcinoma of prostate, Neuroendocrine carcinoma of the bladder, Neuroendocrine carcinoma of the cervix, Neuroendocrine carcinoma of the oesophagus, Neuroendocrine carcinoma of the skin, Neuroendocrine tumour, Neuroendocrine tumour of the lung, Neuroendocrine tumour of the lung metastatic, Neuroendocrine tumour of the rectum, Neurofibrosarcoma, Neurofibrosarcoma metastatic, Neurofibrosarcoma recurrent, Neurogenic tumour, Neurotensinoma, Nipple neoplasm, Nodal marginal zone B-cell lymphoma, Nodal marginal zone B-cell

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Safety Topic	Preferred Term
	lymphoma recurrent, Nodal marginal zone B-cell lymphoma refractory, Nodal marginal zone B-cell lymphoma stage I, Nodal marginal zone B-cell lymphoma stage II, Nodal marginal zone B-cell lymphoma stage III, Nodal marginal zone B-cell lymphoma stage IV, Nodular lymphocyte predominant Hodgkin lymphoma, Nodular melanoma, Non-Hodgkin's lymphoma, Non-Hodgkin's lymphoma metastatic, Non-Hodgkin's lymphoma recurrent, Non-Hodgkin's lymphoma refractory, Non-Hodgkin's lymphoma stage I, Non-Hodgkin's lymphoma stage II, Non-Hodgkin's lymphoma stage III, Non-Hodgkin's lymphoma stage IV, Non-Hodgkin's lymphoma transformed recurrent, Non-Hodgkin's lymphoma unspecified histology aggressive, Non-Hodgkin's lymphoma unspecified histology aggressive recurrent, Non-Hodgkin's lymphoma unspecified histology aggressive refractory, Non-Hodgkin's lymphoma unspecified histology aggressive stage I, Non-Hodgkin's lymphoma unspecified histology aggressive stage II, Non-Hodgkin's lymphoma unspecified histology aggressive stage III, Non-Hodgkin's lymphoma unspecified histology aggressive stage IV, Non-Hodgkin's lymphoma unspecified histology indolent, Non-Hodgkin's lymphoma unspecified histology indolent stage I, Non-Hodgkin's lymphoma unspecified histology indolent stage II, Non-Hodgkin's lymphoma unspecified histology indolent stage III, Non-Hodgkin's lymphoma unspecified histology indolent stage IV, Non-renal cell carcinoma of kidney, Non-secretory adenoma of pituitary, Non-small cell lung cancer, Non-small cell lung cancer metastatic, Non-small cell lung cancer recurrent, Non-small cell lung cancer stage 0, Non-small cell lung cancer stage I, Non-small cell lung cancer stage II, Non-small cell lung cancer stage III, Non-small cell lung cancer stage IIIA, Non-small cell lung cancer stage IIIB, Non-small cell lung cancer stage IV, Nongerminomatous germ cell tumour of the CNS, Nonkeratinising carcinoma of nasopharynx, Ocular cancer metastatic, Ocular haemangiopericytoma, Ocular lymphoma, Ocular melanoma, Ocular neoplasm, Ocular surface squamous neoplasia, Oesophageal adenocarcinoma, Oesophageal adenocarcinoma recurrent, Oesophageal adenocarcinoma stage 0, Oesophageal adenocarcinoma stage I, Oesophageal adenocarcinoma stage II, Oesophageal adenocarcinoma stage III, Oesophageal adenocarcinoma stage IV, Oesophageal adenosquamous carcinoma, Oesophageal cancer metastatic, Oesophageal carcinoma, Oesophageal carcinoma recurrent, Oesophageal carcinoma stage 0, Oesophageal neoplasm, Oesophageal squamous cell carcinoma, Oesophageal squamous cell carcinoma metastatic, Oesophageal squamous cell carcinoma recurrent, Oesophageal squamous cell carcinoma stage 0, Oesophageal squamous cell carcinoma stage I, Oesophageal squamous cell carcinoma stage II, Oesophageal squamous cell carcinoma stage III, Oesophageal squamous cell carcinoma stage IV, Oligoastrocytoma, Oligodendroglioma, Omenn syndrome, Optic glioma, Optic nerve neoplasm, Oral cavity cancer metastatic, Oral neoplasm, Oropharyngeal cancer, Oropharyngeal cancer recurrent, Oropharyngeal cancer stage 0, Oropharyngeal cancer stage I, Oropharyngeal cancer stage II, Oropharyngeal cancer stage III, Oropharyngeal cancer stage IV, Oropharyngeal lymphoepithelioma, Oropharyngeal neoplasm, Oropharyngeal squamous cell carcinoma, Osteosarcoma, Osteosarcoma metastatic, Osteosarcoma recurrent, Ota's naevus, Otic cancer metastatic, Ovarian Sertoli-Leydig cell tumour, Ovarian cancer, Ovarian cancer metastatic, Ovarian cancer recurrent, Ovarian cancer stage I, Ovarian cancer stage II, Ovarian cancer stage III, Ovarian cancer stage IV, Ovarian clear cell carcinoma, Ovarian dysgerminoma stage I, Ovarian dysgerminoma stage II, Ovarian dysgerminoma stage III, Ovarian dysgerminoma stage IV, Ovarian dysgerminoma stage unspecified, Ovarian embryonal carcinoma, Ovarian endometrioid carcinoma, Ovarian epithelial cancer, Ovarian epithelial cancer metastatic, Ovarian epithelial cancer recurrent, Ovarian epithelial cancer stage I, Ovarian epithelial cancer stage II, Ovarian epithelial cancer stage III, Ovarian epithelial cancer stage IV, Ovarian germ cell cancer, Ovarian germ cell cancer stage I, Ovarian germ cell cancer stage II, Ovarian germ cell cancer stage III, Ovarian germ cell cancer stage IV, Ovarian germ cell choriocarcinoma, Ovarian germ cell choriocarcinoma stage I, Ovarian germ cell choriocarcinoma stage II, Ovarian germ cell choriocarcinoma stage III, Ovarian germ cell choriocarcinoma stage IV, Ovarian germ cell embryonal carcinoma stage I, Ovarian germ cell embryonal carcinoma stage II, Ovarian germ cell embryonal carcinoma stage III, Ovarian germ cell embryonal carcinoma stage IV, Ovarian germ cell endodermal sinus tumour, Ovarian germ cell endodermal sinus tumour stage I, Ovarian germ cell endodermal sinus tumour stage II, Ovarian germ cell endodermal sinus tumour stage III, Ovarian germ cell endodermal sinus tumour stage IV, Ovarian germ cell polyembryoma, Ovarian germ cell polyembryoma stage I, Ovarian germ cell polyembryoma stage II, Ovarian germ cell polyembryoma stage III, Ovarian germ cell polyembryoma stage IV, Ovarian germ cell teratoma, Ovarian germ cell teratoma stage I, Ovarian germ cell teratoma stage II, Ovarian germ cell teratoma stage III, Ovarian germ cell teratoma stage IV,

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Safety Topic	Preferred Term
	Ovarian germ cell tumour, Ovarian germ cell tumour mixed, Ovarian granulosa cell tumour, Ovarian granulosa-theca cell tumour, Ovarian low malignant potential tumour, Ovarian melanoma, Ovarian neoplasm, Ovarian stromal cancer, Ovarian theca cell tumour, PD-L1 positive cancer, PD-L2 positive cancer, POEMS syndrome, Paget's disease of nipple, Paget's disease of penis, Paget's disease of the vulva, Pancoast's tumour, Pancreatic carcinoma, Pancreatic carcinoma metastatic, Pancreatic carcinoma recurrent, Pancreatic carcinoma stage 0, Pancreatic carcinoma stage I, Pancreatic carcinoma stage II, Pancreatic carcinoma stage III, Pancreatic carcinoma stage IV, Pancreatic neoplasm, Pancreatic neuroendocrine tumour, Pancreatic neuroendocrine tumour metastatic, Pancreatic sarcoma, Pancreatoblastoma, Papillary renal cell carcinoma, Papillary serous endometrial carcinoma, Papillary thyroid cancer, Paraganglion neoplasm, Paraganglion neoplasm malignant, Paranasal sinus and nasal cavity malignant neoplasm, Paranasal sinus and nasal cavity malignant neoplasm recurrent, Paranasal sinus and nasal cavity malignant neoplasm stage 0, Paranasal sinus and nasal cavity malignant neoplasm stage I, Paranasal sinus and nasal cavity malignant neoplasm stage II, Paranasal sinus and nasal cavity malignant neoplasm stage III, Paranasal sinus and nasal cavity malignant neoplasm stage IV, Paranasal sinus neoplasm, Paraproteinaemia, Parathyroid tumour, Parathyroid tumour malignant, Pelvic neoplasm, Penile cancer, Penile neoplasm, Penile squamous cell carcinoma, Penis carcinoma metastatic, Penis carcinoma recurrent, Penis carcinoma stage I, Penis carcinoma stage II, Penis carcinoma stage III, Penis carcinoma stage IV, Pericardial mesothelioma malignant, Pericardial mesothelioma malignant recurrent, Pericardial neoplasm, Perineal cyst, Peripheral T-cell lymphoma unspecified, Peripheral T-cell lymphoma unspecified recurrent, Peripheral T-cell lymphoma unspecified refractory, Peripheral T-cell lymphoma unspecified stage I, Peripheral T-cell lymphoma unspecified stage II, Peripheral T-cell lymphoma unspecified stage III, Peripheral T-cell lymphoma unspecified stage IV, Peripheral nervous system neoplasm, Peripheral neuroepithelioma of bone, Peripheral neuroepithelioma of bone metastatic, Peripheral neuroepithelioma of bone recurrent, Peripheral neuroepithelioma of soft tissue, Peripheral primitive neuroectodermal bone tumour, Peripheral primitive neuroectodermal tumour of soft tissue, Peritoneal carcinoma metastatic, Peritoneal cyst, Peritoneal gliomatosis, Peritoneal mesothelioma malignant, Peritoneal mesothelioma malignant recurrent, Peritoneal neoplasm, Peritoneal sarcoma, Perivascular epithelioid cell tumour, Phaeochromocytoma, Phaeochromocytoma crisis, Phaeochromocytoma malignant, Pharyngeal cancer, Pharyngeal cancer metastatic, Pharyngeal cancer recurrent, Pharyngeal cancer stage 0, Pharyngeal cancer stage I, Pharyngeal cancer stage II, Pharyngeal cancer stage III, Pharyngeal cancer stage IV, Pharyngeal neoplasm, Philadelphia positive acute lymphocytic leukaemia, Philadelphia positive chronic myeloid leukaemia, Phyllodes tumour, Pigmented epithelioid melanocytoma, Pilomatrix carcinoma, Pineal germinoma, Pineal neoplasm, Pineal parenchymal neoplasm malignant, Pinealoblastoma, Pinealoma, Pineocytoma, Pituicytoma, Pituitary cancer metastatic, Pituitary neoplasm malignant recurrent, Pituitary tumour, Pituitary tumour recurrent, Placental neoplasm, Plasma cell leukaemia, Plasma cell leukaemia in remission, Plasma cell myeloma, Plasma cell myeloma in remission, Plasma cell myeloma recurrent, Plasma cell myeloma refractory, Plasmablastic lymphoma, Plasmacytoma, Pleomorphic leiomyosarcoma, Pleomorphic liposarcoma, Pleural mesothelioma, Pleural mesothelioma malignant, Pleural mesothelioma malignant recurrent, Pleural neoplasm, Pleural sarcoma, Pleuropulmonary blastoma, Polycythaemia vera, Poorly differentiated thyroid carcinoma, Porocarcinoma, Post transplant lymphoproliferative disorder, Postcricoid cancer, Precursor B-lymphoblastic lymphoma, Precursor B-lymphoblastic lymphoma recurrent, Precursor B-lymphoblastic lymphoma refractory, Precursor B-lymphoblastic lymphoma stage I, Precursor B-lymphoblastic lymphoma stage II, Precursor B-lymphoblastic lymphoma stage III, Precursor B-lymphoblastic lymphoma stage IV, Precursor T-lymphoblastic leukaemia acute, Precursor T-lymphoblastic lymphoma/leukaemia, Precursor T-lymphoblastic lymphoma/leukaemia recurrent, Precursor T-lymphoblastic lymphoma/leukaemia refractory, Precursor T-lymphoblastic lymphoma/leukaemia stage I, Precursor T-lymphoblastic lymphoma/leukaemia stage II, Precursor T-lymphoblastic lymphoma/leukaemia stage III, Precursor T-lymphoblastic lymphoma/leukaemia stage IV, Primary breast lymphoma, Primary cardiac lymphoma, Primary cutaneous adenoid cystic carcinoma, Primary effusion lymphoma, Primary gastrointestinal follicular lymphoma, Primary mediastinal large B-cell lymphoma, Primary mediastinal large B-cell lymphoma recurrent, Primary mediastinal large B-cell lymphoma refractory, Primary mediastinal large B-cell lymphoma stage I, Primary mediastinal large B-cell lymphoma stage II, Primary mediastinal large B-cell lymphoma stage III, Primary mediastinal large

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Safety Topic	Preferred Term
	B-cell lymphoma stage IV, Primary myelofibrosis, Primary pulmonary melanoma, Primitive neuroectodermal tumour, Primitive neuroectodermal tumour metastatic, Prolactin-producing pituitary tumour, Prolymphocytic leukaemia, Prostate cancer, Prostate cancer metastatic, Prostate cancer recurrent, Prostate cancer stage 0, Prostate cancer stage I, Prostate cancer stage II, Prostate cancer stage III, Prostate cancer stage IV, Prostate sarcoma, Pseudo Richter's syndrome, Pseudosarcoma, Queyrat erythroplasia, RET gene fusion cancer, Rectal adenocarcinoma, Rectal cancer, Rectal cancer metastatic, Rectal cancer recurrent, Rectal cancer stage 0, Rectal cancer stage I, Rectal cancer stage II, Rectal cancer stage III, Rectal cancer stage IV, Rectal neoplasm, Rectosigmoid cancer, Rectosigmoid cancer metastatic, Rectosigmoid cancer recurrent, Rectosigmoid cancer stage 0, Rectosigmoid cancer stage I, Rectosigmoid cancer stage II, Rectosigmoid cancer stage III, Rectosigmoid cancer stage IV, Recurrent N-ras mutation-positive colorectal carcinoma, Recurrent cancer, Refractory cancer, Renal cancer, Renal cancer metastatic, Renal cancer recurrent, Renal cancer stage I, Renal cancer stage II, Renal cancer stage III, Renal cancer stage IV, Renal cell carcinoma, Renal cell carcinoma recurrent, Renal cell carcinoma stage I, Renal cell carcinoma stage II, Renal cell carcinoma stage III, Renal cell carcinoma stage IV, Renal neoplasm, Respiratory tract carcinoma in situ, Respiratory tract neoplasm, Retinal melanoma, Retinal neoplasm, Retinoblastoma, Retro-orbital neoplasm, Retroperitoneal cancer, Retroperitoneal neoplasm, Retroperitoneal neoplasm metastatic, Rhabdoid tumour, Rhabdoid tumour of the kidney, Rhabdomyosarcoma, Rhabdomyosarcoma recurrent, Richter's syndrome, Rosai-Dorfman syndrome, Round cell liposarcoma, Salivary gland cancer, Salivary gland cancer recurrent, Salivary gland cancer stage 0, Salivary gland cancer stage I, Salivary gland cancer stage II, Salivary gland cancer stage III, Salivary gland cancer stage IV, Salivary gland neoplasm, Sarcoma, Sarcoma metastatic, Sarcoma of skin, Sarcoma uterus, Sarcomatoid carcinoma, Sarcomatoid carcinoma of the lung, Sarcomatoid mesothelioma, Sarcomatosis, Schwannoma, Sclerosing epithelioid fibrosarcoma, Scrotal cancer, Sebaceous carcinoma, Second primary malignancy, Secretory adenoma of pituitary, Secretory breast carcinoma, Seminoma, Serous cystadenocarcinoma ovary, Serrated polyposis syndrome, Sertoli cell testicular tumour, Signet-ring cell carcinoma, Sinus cancer metastatic, Skin angiosarcoma, Skin cancer, Skin cancer metastatic, Skin neoplasm bleeding, Skin squamous cell carcinoma metastatic, Skin squamous cell carcinoma recurrent, Skull base tumour, Small cell carcinoma, Small cell carcinoma of the cervix, Small cell lung cancer, Small cell lung cancer extensive stage, Small cell lung cancer limited stage, Small cell lung cancer metastatic, Small cell lung cancer recurrent, Small intestine adenocarcinoma, Small intestine carcinoma, Small intestine carcinoma metastatic, Small intestine carcinoma recurrent, Small intestine carcinoma stage 0, Small intestine carcinoma stage I, Small intestine carcinoma stage II, Small intestine carcinoma stage III, Small intestine carcinoma stage IV, Small intestine leiomyosarcoma, Small intestine neuroendocrine tumour, Smooth muscle cell neoplasm, Smouldering systemic mastocytosis, Soft tissue neoplasm, Soft tissue sarcoma, Solid pseudopapillary tumour of the pancreas, Solitary epithelioid histiocytoma, Solitary fibrous tumour, Somatostatinoma, Spermatocytic seminoma, Spinal cord neoplasm, Spinal meningioma malignant, Spinal nerve sheath tumour, Spindle cell sarcoma, Splenic cyst, Splenic hamartoma, Splenic marginal zone lymphoma, Splenic marginal zone lymphoma recurrent, Splenic marginal zone lymphoma refractory, Splenic marginal zone lymphoma stage I, Splenic marginal zone lymphoma stage II, Splenic marginal zone lymphoma stage III, Splenic marginal zone lymphoma stage IV, Splenic neoplasm malignancy unspecified, Squamoproliferative lesion, Squamous cell breast carcinoma, Squamous cell carcinoma, Squamous cell carcinoma of head and neck, Squamous cell carcinoma of lung, Squamous cell carcinoma of pharynx, Squamous cell carcinoma of skin, Squamous cell carcinoma of the cervix, Squamous cell carcinoma of the hypopharynx, Squamous cell carcinoma of the oral cavity, Squamous cell carcinoma of the parotid gland, Squamous cell carcinoma of the tongue, Squamous cell carcinoma of the vagina, Squamous cell carcinoma of the vulva, Squamous endometrial carcinoma, Stewart-Treves syndrome, Superficial spreading melanoma stage I, Superficial spreading melanoma stage II, Superficial spreading melanoma stage III, Superficial spreading melanoma stage IV, Superficial spreading melanoma stage unspecified, Synovial sarcoma, Synovial sarcoma metastatic, Synovial sarcoma recurrent, Systemic mastocytosis, T-cell chronic lymphocytic leukaemia, T-cell lymphoma, T-cell lymphoma recurrent, T-cell lymphoma refractory, T-cell lymphoma stage I, T-cell lymphoma stage II, T-cell lymphoma stage III, T-cell lymphoma stage IV, T-cell lymphoma unclassifiable, T-cell prolymphocytic leukaemia, T-cell type acute leukaemia, T-cell unclassifiable lymphoma high grade, T-cell unclassifiable lymphoma low grade, TEMPI syndrome, Tendon neoplasm, Teratoma, Testicular cancer metastatic,

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Safety Topic	Preferred Term
	Testicular choriocarcinoma, Testicular choriocarcinoma recurrent, Testicular choriocarcinoma stage I, Testicular choriocarcinoma stage II, Testicular choriocarcinoma stage III, Testicular embryonal carcinoma, Testicular embryonal carcinoma stage I, Testicular embryonal carcinoma stage II, Testicular embryonal carcinoma stage III, Testicular germ cell cancer, Testicular germ cell cancer metastatic, Testicular germ cell tumour, Testicular germ cell tumour mixed, Testicular germ cell tumour mixed stage I, Testicular germ cell tumour mixed stage II, Testicular germ cell tumour mixed stage III, Testicular leiomyosarcoma, Testicular malignant teratoma, Testicular malignant teratoma stage I, Testicular malignant teratoma stage II, Testicular malignant teratoma stage III, Testicular neoplasm, Testicular seminoma (pure), Testicular seminoma (pure) stage I, Testicular seminoma (pure) stage II, Testicular seminoma (pure) stage III, Testicular yolk sac tumour, Testicular yolk sac tumour stage I, Testicular yolk sac tumour stage II, Testicular yolk sac tumour stage III, Testis cancer, Testis cancer recurrent, Throat cancer, Thymic cancer metastatic, Thymic carcinoma, Thymoma, Thymoma malignant, Thymoma malignant recurrent, Thyroid B-cell lymphoma, Thyroid cancer, Thyroid cancer metastatic, Thyroid cancer recurrent, Thyroid cancer stage 0, Thyroid cancer stage I, Thyroid cancer stage II, Thyroid cancer stage III, Thyroid cancer stage IV, Thyroid neoplasm, Thyroid stimulating hormone-producing pituitary tumour, Tongue cancer metastatic, Tongue cancer recurrent, Tongue carcinoma stage 0, Tongue carcinoma stage I, Tongue carcinoma stage II, Tongue carcinoma stage III, Tongue carcinoma stage IV, Tongue neoplasm, Tongue neoplasm malignant stage unspecified, Tonsil cancer, Tonsil cancer metastatic, Tonsillar neoplasm, Tracheal cancer, Tracheal neoplasm, Transformation to acute myeloid leukaemia, Transitional cell cancer of renal pelvis and ureter metastatic, Transitional cell cancer of the renal pelvis and ureter, Transitional cell cancer of the renal pelvis and ureter localised, Transitional cell cancer of the renal pelvis and ureter recurrent, Transitional cell cancer of the renal pelvis and ureter regional, Transitional cell carcinoma, Transitional cell carcinoma metastatic, Transitional cell carcinoma recurrent, Transitional cell carcinoma urethra, Trichoblastic carcinoma, Triple hit lymphoma, Triple negative breast cancer, Triple positive breast cancer, Trisomy 12, Tubular breast carcinoma, Tumour budding, Tumour hyperprogression, Tumour invasion, Tumour of ampulla of Vater, Undifferentiated carcinoma of colon, Undifferentiated nasopharyngeal carcinoma, Undifferentiated sarcoma, Ureteral neoplasm, Ureteric cancer, Ureteric cancer local, Ureteric cancer metastatic, Ureteric cancer recurrent, Ureteric cancer regional, Urethral cancer, Urethral cancer metastatic, Urethral cancer recurrent, Urethral melanoma metastatic, Urethral neoplasm, Urinary bladder sarcoma, Urinary tract carcinoma in situ, Urinary tract neoplasm, Uterine cancer, Uterine carcinoma in situ, Uterine cervix lymphoma, Uterine leiomyosarcoma, Uterine neoplasm, Uveal melanoma, Vaginal adenocarcinoma, Vaginal cancer, Vaginal cancer metastatic, Vaginal cancer recurrent, Vaginal cancer stage 0, Vaginal cancer stage I, Vaginal cancer stage II, Vaginal cancer stage III, Vaginal cancer stage IVA, Vaginal cancer stage IVB, Vaginal neoplasm, Vascular neoplasm, Vipoma, Vulval cancer, Vulval cancer metastatic, Vulval cancer recurrent, Vulval cancer stage 0, Vulval cancer stage I, Vulval cancer stage II, Vulval cancer stage III, Vulval cancer stage IV, Vulval neoplasm, Vulvar adenocarcinoma, Vulvar basal cell carcinoma, Waldenstrom's macroglobulinaemia, Waldenstrom's macroglobulinaemia recurrent, Waldenstrom's macroglobulinaemia refractory, Waldenstrom's macroglobulinaemia stage I, Waldenstrom's macroglobulinaemia stage II, Waldenstrom's macroglobulinaemia stage III, Waldenstrom's macroglobulinaemia stage IV, X-linked lymphoproliferative syndrome, Xanthogranuloma, Yolk sac tumour site unspecified

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8.2. Preferred Term to identify Adverse Event of Special Interest (AESI) for Alpelisib

Safety Topic	Preferred Term
GI toxicity Nausea Vomiting Diarrhea	Acetonaemic vomiting, Acute vestibular syndrome, Cannabinoid hyperemesis syndrome, Cyclic vomiting syndrome, Dialysis disequilibrium syndrome, Diarrhoea, Diarrhoea haemorrhagic, Discoloured vomit, Faecal vomiting, Hyperemesis gravidarum, Infantile diarrhoea, Infantile spitting up, Infantile vomiting, Meniere's disease, Morning sickness, Nausea, Post procedural diarrhoea, Post-tussive vomiting, Procedural nausea, Procedural vomiting, Regurgitation, Retching, Vomiting, Vomiting projectile, Vomiting psychogenic
Hyperglycaemia	Acquired generalised lipodystrophy, Alpha hydroxybutyric acid increased, Blood 1,5-anhydroglucitol decreased, Blood glucose increased, Diabetes complicating pregnancy, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Diabetic arteritis, Diabetic coma, Diabetic coronary microangiopathy, Diabetic hepatopathy, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Diabetic ketosis, Diabetic metabolic decompensation, Diabetic wound, Euglycaemic diabetic ketoacidosis, Fructosamine increased, Fulminant type 1 diabetes mellitus, Gestational diabetes, Glucose tolerance impaired, Glucose tolerance impaired in pregnancy, Glucose urine present, Glycated albumin increased, Glycated serum protein increased, Glycosuria, Glycosuria during pregnancy, Glycosylated haemoglobin abnormal, Glycosylated haemoglobin increased, Hepatogenous diabetes, Hyperglycaemia, Hyperglycaemic crisis, Hyperglycaemic hyperosmolar nonketotic syndrome, Hyperglycaemic seizure, Hyperglycaemic unconsciousness, Impaired fasting glucose, Insulin resistance, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Ketoacidosis, Ketonuria, Ketosis, Ketosis-prone diabetes mellitus, Latent autoimmune diabetes in adults, Maternally inherited diabetes and deafness, Monogenic diabetes, Neonatal diabetes mellitus, Neonatal hyperglycaemia, New onset diabetes after transplantation, Pancreatogenous diabetes, Pseudodiabetes, Steroid diabetes, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Type 3 diabetes mellitus, Urine ketone body present
Hypersensitivity and anaphylactic reaction	Administration site dermatitis, Administration site eczema, Administration site hypersensitivity, Administration site rash, Administration site recall reaction, Administration site urticaria, Administration site vasculitis, Allergic bronchitis, Allergic colitis, Allergic cough, Allergic cystitis, Allergic eosinophilia, Allergic gastroenteritis, Allergic hepatitis, Allergic keratitis, Allergic oedema, Allergic otitis externa, Allergic otitis media, Allergic pharyngitis, Allergic respiratory disease, Allergic respiratory symptom, Allergic sinusitis, Allergic transfusion reaction, Allergy alert test positive, Allergy test positive, Allergy to immunoglobulin therapy, Allergy to vaccine, Anaphylactic reaction, Anaphylactic shock, Anaphylactic transfusion reaction, Anaphylactoid reaction, Anaphylactoid shock, Anaphylaxis treatment, Angioedema, Anti-neutrophil cytoplasmic antibody positive vasculitis, Antiallergic therapy, Antiendomysial antibody positive, Application site dermatitis, Application site eczema, Application site hypersensitivity, Application site rash, Application site recall reaction, Application site urticaria, Application site vasculitis, Arthritis allergic, Atopy, Blepharitis allergic, Blood immunoglobulin E abnormal, Blood immunoglobulin E increased, Bromoderma, Bronchospasm, Bullous erysipelas, Bullous haemorrhagic dermatosis, Catheter site dermatitis, Catheter site eczema, Catheter site hypersensitivity, Catheter site rash, Catheter site urticaria, Catheter site vasculitis, Chronic eosinophilic rhinosinusitis, Chronic hyperplastic eosinophilic sinusitis, Circulatory collapse, Circumoral oedema, Conjunctival oedema, Conjunctivitis allergic, Contact stomatitis, Contrast media allergy, Contrast media reaction, Corneal oedema, Dennie-Morgan fold, Dermatitis allergic, Dermatitis atopic, Dermatitis contact, Dermatitis herpetiformis, Dermatitis infected, Dialysis membrane reaction, Distributive shock, Documented hypersensitivity to administered product, Drug hypersensitivity, Drug provocation test, Eczema, Eczema herpeticum, Eczema infantile, Eczema nummular, Eczema vaccinatum, Eczema vesicular, Eczema weeping, Encephalitis allergic, Encephalopathy allergic, Epidermolysis, Epidermolysis bullosa, Epiglottic oedema, Erythema nodosum, Eye allergy, Eye oedema, Eye swelling, Eyelid oedema, Face oedema, Giant papillary conjunctivitis, Gingival oedema, Gingival swelling, Gleich's syndrome, Haemorrhagic urticaria, Hand dermatitis, Henoch-Schonlein purpura, Henoch-Schonlein purpura nephritis, Heparin-induced thrombocytopenia, Hereditary angioedema, Hypersensitivity, Hypersensitivity vasculitis, Hypotensive crisis, Idiopathic urticaria, Immediate post-injection reaction, Immune thrombocytopenia, Immune tolerance induction, Immune-mediated adverse reaction, Implant

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Safety Topic	Preferred Term
	site dermatitis, Implant site hypersensitivity, Implant site rash, Implant site urticaria, Incision site dermatitis, Incision site rash, Infusion site dermatitis, Infusion site eczema, Infusion site hypersensitivity, Infusion site rash, Infusion site recall reaction, Infusion site urticaria, Infusion site vasculitis, Injection site dermatitis, Injection site eczema, Injection site hypersensitivity, Injection site rash, Injection site recall reaction, Injection site urticaria, Injection site vasculitis, Instillation site hypersensitivity, Instillation site rash, Instillation site urticaria, Interstitial granulomatous dermatitis, Intestinal angioedema, Iodine allergy, Kounis syndrome, Laryngeal oedema, Laryngitis allergic, Laryngospasm, Laryngotracheal oedema, Limbal swelling, Lip oedema, Lip swelling, Mast cell degranulation present, Medical device site dermatitis, Medical device site eczema, Medical device site hypersensitivity, Medical device site rash, Medical device site recall reaction, Medical device site urticaria, Mouth swelling, Multiple allergies, Multiple drug hypersensitivity, NSAID exacerbated respiratory disease, Nephritis allergic, Nikolsky's sign, Oculorespiratory syndrome, Oedema mouth, Oral allergy syndrome, Oropharyngeal blistering, Oropharyngeal spasm, Oropharyngeal swelling, Palatal oedema, Palatal swelling, Palisaded neutrophilic granulomatous dermatitis, Palpable purpura, Pathergy reaction, Periorbital oedema, Pharyngeal oedema, Pruritus allergic, Radioallergosorbent test positive, Rash neonatal, Rash rubelliform, Rash scarlatiniform, Reaction to azo-dyes, Reaction to colouring, Reaction to preservatives, Rhinitis allergic, Scleral oedema, Scleritis allergic, Scrotal oedema, Serum sickness, Serum sickness-like reaction, Shock, Shock symptom, Skin reaction, Skin test positive, Solar urticaria, Solvent sensitivity, Stoma site hypersensitivity, Stoma site rash, Swelling face, Swollen tongue, Tongue oedema, Tracheal oedema, Type I hypersensitivity, Type II hypersensitivity, Type III immune complex mediated reaction, Type IV hypersensitivity reaction, Urticaria, Urticaria cholinergic, Urticaria chronic, Urticaria contact, Urticaria papular, Urticaria physical, Urticaria pigmentosa, Urticaria vesiculosa, Urticarial vasculitis, Vaccination site dermatitis, Vaccination site eczema, Vaccination site exfoliation, Vaccination site hypersensitivity, Vaccination site rash, Vaccination site recall reaction, Vaccination site urticaria, Vaccination site vasculitis, Vaccination site vesicles, Vaginal ulceration, Vancomycin infusion reaction, Vasculitic rash, Vessel puncture site rash, Vulval ulceration, Vulvovaginal exfoliation, Vulvovaginal ulceration
Osteonecrosis of jaw	Osteonecrosis, Osteonecrosis of jaw
Pancreatitis	Amylase abnormal, Amylase creatinine clearance ratio abnormal, Amylase increased, Blood trypsin increased, Cullen's sign, Grey Turner's sign, Haemorrhagic necrotic pancreatitis, Hereditary pancreatitis, Hyperamylasaemia, Hyperlipasaemia, Idiopathic pancreatitis, Immune-mediated pancreatitis, Ischaemic pancreatitis, Lipase abnormal, Lipase increased, Lipase urine increased, Obstructive pancreatitis, Oedematous pancreatitis, Pancreatic abscess, Pancreatic duct rupture, Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, Pancreatic enzymes increased, Pancreatic haemorrhage, Pancreatic phlegmon, Pancreatic pseudoaneurysm, Pancreatic pseudocyst, Pancreatic pseudocyst drainage, Pancreatic pseudocyst haemorrhage, Pancreatic pseudocyst rupture, Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatitis relapsing, Pancreatorenal syndrome, Peripancreatic fluid collection, Subacute pancreatitis
Pneumonitis	Acute interstitial pneumonitis, Alveolar lung disease, Alveolar proteinosis, Alveolitis, Alveolitis necrotising, Autoimmune lung disease, Bronchiolitis, Bronchiolitis obliterans syndrome, Chronic graft versus host disease in lung, Combined pulmonary fibrosis and emphysema, Confirmed e-cigarette or vaping product use associated lung injury, Diffuse alveolar damage, Eosinophilia myalgia syndrome, Eosinophilic granulomatosis with polyangiitis, Eosinophilic pneumonia, Eosinophilic pneumonia acute, Eosinophilic pneumonia chronic, Hypersensitivity pneumonitis, Idiopathic interstitial pneumonia, Idiopathic pneumonia syndrome, Idiopathic pulmonary fibrosis, Immune-mediated lung disease, Interstitial lung abnormality, Interstitial lung disease, Low lung compliance, Lung infiltration, Lung opacity, Necrotising bronchiolitis, Obliterative bronchiolitis, Pleuroparenchymal fibroelastosis, Pneumonitis, Probable e-cigarette or vaping product use associated lung injury, Progressive massive fibrosis, Pulmonary fibrosis, Pulmonary necrosis, Pulmonary radiation injury, Pulmonary toxicity, Pulmonary vasculitis, Radiation alveolitis, Radiation bronchitis, Radiation fibrosis - lung, Radiation pneumonitis, Rheumatoid arthritis-associated interstitial lung disease, Small airways disease, Transfusion-related acute lung injury
Rash	Dermatitis, Dermatitis acneiform, Dermatitis psoriasiform, Drug eruption, Eyelid rash, Genital rash, Mucocutaneous rash, Nodular rash, Perineal rash, Rash, Rash erythematous, Rash follicular, Rash

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Safety Topic	Preferred Term
	macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash papular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Vulvovaginal rash
Severe cutaneous reactions	AGEP-DRESS overlap, Acute generalised exanthematous pustulosis, Bullous haemorrhagic dermatosis, Cutaneous vasculitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Drug reaction with eosinophilia and systemic symptoms, Epidermal necrosis, Erythema multiforme, Erythrodermic atopic dermatitis, Exfoliative rash, Generalised bullous fixed drug eruption, Oculomucocutaneous syndrome, SJS-TEN overlap, Severe cutaneous adverse reaction, Skin necrosis, Stevens-Johnson syndrome, Target skin lesion, Toxic epidermal necrolysis, Toxic skin eruption

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

8.3. Laboratory parameters and corresponding CTCAE v4.03 Term that will be considered in the analysis

Laboratory parameter (Unit)	Directional toxicity grade	CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade	Grade definition v4.03
Hematology (Screening, C1D15, C2D1, C2D15, C3D1, C4D1, C5D1, C6D1, D1 every 3 cycles starting with C9, EOT)					
WBC or White Blood Cells (10^9/L)	LOW	Investigations	White blood cell decreased	Grade 1	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L
				Grade 2	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L
				Grade 3	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L
				Grade 4	<1000/mm3; <1.0 x 10e9 /L
				Grade 5	-
	HIGH	Blood and lymphatic system disorders	Leukocytosis	Grade 1	-
				Grade 2	-
				Grade 3	>100,000/mm3
				Grade 4	Clinical manifestations of leucostasis; urgent intervention indicated
				Grade 5	Death
ANC (absolute neutrophil count) or Neutrophils* (10^9/L)	LOW	Investigations	Neutrophil count decreased	Grade 1	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L
				Grade 2	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L
				Grade 3	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L
				Grade 4	<500/mm3; <0.5 x 10e9 /L
				Grade 5	-
	HIGH	NP	NP	NP	NP
Lymphocytes (absolute) or Lymphocytes* (10^9/L)	LOW	Investigations	Lymphocyte count decreased	Grade 1	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L
				Grade 2	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L
				Grade 3	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L
				Grade 4	<200/mm3; <0.2 x 10e9 /L
				Grade 5	-
	HIGH	Investigations	Lymphocyte count increased	Grade 1	-
				Grade 2	>4000/mm3 - 20,000/mm3
				Grade 3	>20,000/mm3
				Grade 4	-
				Grade 5	-
Hemoglobin (g/L)	LOW	Blood and lymphatic system disorders	Anemia	Grade 1	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

				Grade 2	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L
				Grade 3	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
				Grade 4	Life-threatening consequences; urgent intervention indicated
				Grade 5	Death
	HIGH	Investigations	Hemoglobin increased	Grade 1	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN
				Grade 2	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN
				Grade 3	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN
				Grade 4	-
				Grade 5	-
Platelets (10^9/L)	LOW	Investigations	Platelet count decreased	Grade 1	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L
				Grade 2	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L
				Grade 3	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L
				Grade 4	<25,000/mm3; <25.0 x 10e9/L
				Grade 5	-
	HIGH	NP	NP	NP	NP
Chemistry (Screening, C1D15, C2D1, C2D15, C3D1, C4D1, C5D1, C6D1, D1 every 3 cycles starting with C9, EOT)					
Alkaline photosphatase (U/L)	LOW	NP	NP	NP	NP
	HIGH	Investigations	Alkaline phosphatase increased	Grade 1	>ULN - 2.5 x ULN
				Grade 2	>2.5 - 5.0 x ULN
				Grade 3	>5.0 - 20.0 x ULN
				Grade 4	>20.0 x ULN
				Grade 5	-
ALT (SGPT) (U/L)	HIGH	Investigations	Alanine aminotransferase increased	Grade 1	>ULN - 3.0 x ULN
				Grade 2	>3.0 - 5.0 x ULN
				Grade 3	>5.0 - 20.0 x ULN
				Grade 4	>20.0 x ULN
				Grade 5	-
AST (SGOT) (U/L)	HIGH	Investigations	Aspartate aminotransferase increased	Grade 1	>ULN - 3.0 x ULN
				Grade 2	>3.0 - 5.0 x ULN
				Grade 3	>5.0 - 20.0 x ULN
				Grade 4	>20.0 x ULN
				Grade 5	-
	LOW		Hypocalcemia	Grade 1	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

Calcium (corrected for serum albumin) (mmol/L)		Metabolism and nutrition disorders			mmol/L; Ionized calcium <LLN - 1.0 mmol/L
				Grade 2	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic
				Grade 3	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated
				Grade 4	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences
				Grade 5	Death
	HIGH	Metabolism and nutrition disorders	Hypercalcemia	Grade 1	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L
				Grade 2	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic
				Grade 3	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated
				Grade 4	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
				Grade 5	Death
Creatinine (µmol/L)	LOW	NP	NP	NP	
	HIGH	Investigations	Creatinine increased	Grade 1	>1 - 1.5 x baseline; >ULN - 1.5 x ULN
				Grade 2	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN
				Grade 3	>3.0 baseline; >3.0 - 6.0 x ULN
				Grade 4	>6.0 x ULN
				Grade 5	-
Potassium (mmol/L)	LOW	Metabolism and nutrition disorders	Hypokalemia	Grade 1	<LLN - 3.0 mmol/L
				Grade 2	<LLN - 3.0 mmol/L; symptomatic; intervention indicated

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

				Grade 3	<3.0-2.5 mmol/L; hospitalization indicated
				Grade 4	<2.5 mmol/L; life-threatening consequences
				Grade 5	Death
	HIGH	Metabolism and nutrition disorders	Hyperkalemia	Grade 1	>ULN - 5.5 mmol/L
				Grade 2	>5.5 - 6.0 mmol/L
				Grade 3	>6.0-7.0 mmol/L; hospitalization indicated
				Grade 4	>7.0 mmol/L; life-threatening consequences
				Grade 5	Death
Sodium (mmol/L)	LOW	Metabolism and nutrition disorders	Hyponatremia	Grade 1	<LLN - 130 mmol/L
				Grade 2	-
				Grade 3	<130 - 120 mmol/L
				Grade 4	<120 mmol/L; life-threatening consequences
				Grade 5	Death
	HIGH	Metabolism and nutrition disorders	Hypernatremia	Grade 1	>ULN - 150 mmol/L
				Grade 2	>150 - 155 mmol/L
				Grade 3	>155-160 mmol/L; hospitalization indicated
				Grade 4	>160 mmol/L; life-threatening consequences
				Grade 5	Death
Magnesium (mmol/L)	LOW	Metabolism and nutrition disorders	Hypomagnesemia	Grade 1	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L
				Grade 2	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L
				Grade 3	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L
				Grade 4	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
				Grade 5	Death
	HIGH	Metabolism and nutrition disorders	Hypermagnesemia	Grade 1	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L
				Grade 2	-
				Grade 3	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L
				Grade 4	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
				Grade 5	Death
Phosphorus (mmol/L)	LOW	Metabolism and nutrition disorders	Hypophosphatemia	Grade 1	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L
				Grade 2	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

				Grade 3	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L
				Grade 4	<1.0 mg/dL; <0.3 mmol/L; lifethreatening consequences
				Grade 5	Death
	HIGH	NP	NP	NP	NP
Total bilirubin (µmol/L)	LOW	NP	NP	NP	NP
	HIGH	Investigations	Blood bilirubin increased	Grade 1	>ULN - 1.5 x ULN
				Grade 2	>1.5 - 3.0 x ULN
				Grade 3	>3.0 - 10.0 x ULN
				Grade 4	>10.0 x ULN
				Grade 5	-
Gamma-glutamyl transpeptidase (GGT) (U/L) ***	LOW	NP	NP	NP	NP
	HIGH	Investigations	GGT increased	Grade 1	>ULN - 2.5 x ULN
				Grade 2	>2.5 - 5.0 x ULN
				Grade 3	>5.0 - 20.0 x ULN
				Grade 4	>20.0 x ULN
				Grade 5	-
Albumin (g/L) ***	LOW	Metabolism and nutrition disorders	Hypoalbuminemia	Grade 1	<LLN - 3 g/dL; <LLN - 30 g/L
				Grade 2	<3 - 2 g/dL; <30 - 20 g/L
				Grade 3	<2 g/dL; <20 g/L
				Grade 4	Life-threatening consequences; urgent intervention indicated
				Grade 5	Death
	HIGH	NP	NP	NP	NP
Creatin-kinase (U/L) ***	HIGH	Investigations	CPK increased	Grade 1	>ULN - 2.5 x ULN
				Grade 2	>2.5 x ULN - 5 x ULN
				Grade 3	>5 x ULN - 10 x ULN
				Grade 4	>10 x ULN
				Grade 5	-
Uric acid (µmol/L) ***	LOW	NP	NP	NP	NP
	HIGH	Metabolism and nutrition disorders	Hyperuricemia	Grade 1	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences
				Grade 2	-
				Grade 3	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
				Grade 4	>10 mg/dL; >0.59 mmol/L; life-threatening consequences
				Grade 5	Death
Plasma glucose (fasting) or Plasma glucose (random) (mmol/L) ***	LOW	Metabolism and nutrition disorders	Hypoglycemia	Grade 1	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L
				Grade 2	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L
				Grade 3	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L

DocuSign Envelope ID: D72BE88D-AB29-47A6-B60A-2E90E6956B91

				Grade 4	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
				Grade 5	Death
	HIGH	Metabolism and nutrition disorders	Hyperglycemia	Grade 1	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L
				Grade 2	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L
				Grade 3	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated
				Grade 4	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
				Grade 5	Death
Total cholesterol (fasting) (mmol/L) ***	HIGH	Investigations	Cholesterol high	Grade 1	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L
				Grade 2	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L
				Grade 3	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L
				Grade 4	>500 mg/dL; >12.92 mmol/L
				Grade 5	-
Triglycerides (fasting) (mmol/L) ***	HIGH	Metabolism and nutrition disorders	Hypertriglyceridemia	Grade 1	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L
				Grade 2	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L
				Grade 3	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L
				Grade 4	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences
				Grade 5	Death
Amylase (fasting) (U/L) ***	HIGH	Investigations	Serum amylase increased	Grade 1	>ULN - 1.5 x ULN
				Grade 2	>1.5 - 2.0 x ULN
				Grade 3	>2.0 - 5.0 x ULN
				Grade 4	>5.0 x ULN
				Grade 5	-
Lipase (fasting) (U/L) ***	HIGH	Investigations	Lipase increased	Grade 1	>ULN - 1.5 x ULN
				Grade 2	>1.5 - 2.0 x ULN
				Grade 3	>2.0 - 5.0 x ULN
				Grade 4	>5.0 x ULN
				Grade 5	-

NP=Not Present.
Text in blue indicates the part of grade definition not considered for the CTCAE grade computation, since referring to clinical assessment or to avoid overlap between different grades.
Of note, in the grade of 'Hemoglobin increased' and 'Creatinine increased' the baseline values will be involved, and the baseline value considered refers to the last available assessment on or before the start date of treatment (i.e., C1D1).

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This means that this baseline value could not be the same value collected at screening in case of unscheduled visit performed between screening and C1D1.
***Only for extension phase.

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